The effect on joint fluid concentration of neuropeptide Y by intra-articular injection of glucocorticoid in temporomandibular joint arthritis

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Twenty-two patients (29 joints) with temporomandibular joint (TMJ) arthritis of specific or unspecific nature were given one intra-articular glucocorticoid (GC) injection. The effect on subjective symptoms and clinical signs in the craniomandibular system and on joint aspirate concentration of neuropeptide Y-like immunoreactivity (NPY-LI) was evaluated at follow-up visits 2–3 or 4–6 weeks after treatment. In the patients with specific inflammatory joint disease the treatment resulted in an improvement of symptoms and clinical signs and in a reduction in the TMJ level of NPY-LI 2–3 weeks after treatment. In the patients with unspecific inflammatory joint disease there was also an improvement in the clinical variables and a reduction in the NPY-LI level after 2–3 weeks, but not on a statistically significant level. The results of this study show that intra-articular GC treatment causes a short-term decrease of the TMJ fluid level of NPY-LI in patients with specific inflammatory joint disease, while symptoms and signs improve.

☐ *Inflammatory joint disease; pain; rheumatoid arthritis; sympathetic nerves; synovial fluid*

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The anti-inflammatory effect of glucocorticoids (GC) on synovial tissues, given systemically or intra-articularly, is well documented (1). Intra-articular GC has proved useful in alleviating pain, swelling, and dysfunction in inflammatory joint diseases such as rheumatoid arthritis (RA) and in primarily non-inflammatory joint diseases such as degenerative joint disease (DJD). The mechanism by which GC exerts its anti-inflammatory action is not entirely understood, including its effects on the release of neuropeptides from nerve fiber terminals. It is known to inhibit the inflammatory reaction by acting on the key mediators of the inflammatory response, the pharmacologically active lipids, such as prostaglandins and leukotrienes. These lipids are the result of the catabolism of arachidonic acid, which in turn is the result of the splitting of phospholipids by the enzyme phospholipase A_2. GC is considered to induce the synthesis of lipocortin, an inhibitory protein of phospholipase A_2, and thereby to block the inflammatory reaction (2).

Patients with long-standing local pain and dysfunction due to arthritis of the temporomandibular joint (TMJ) have been subjected to intra-articular GC injections after failure of more conservative treatment (3). The results show that intra-articular injections of GC combined with a local anesthetic may have a long-term palliative effect on subjective symptoms and clinical signs from the joint (4). In a clinical trial of methylprednisolone (Depo-Medrol®) for RA of the TMJ it was shown that this drug had a significant short-term effect (4–5 weeks) on both subjective symptoms and clinical signs exceeding that of saline (5).

There is considerable evidence that certain neuropeptides take part in the inflammatory process leading to joint pain and destruction in arthritis. Neuropeptide Y (NPY) was investigated in this study because it has been suggested to be a modulator of arthritis and, in addition, has a long-lasting vasoconstrictive effect. Low intra-articular temperature (IAT) and, accordingly, impaired blood flow of the TMJ in human chronic RA has been shown to be frequent and associated with high joint aspirate concentration of NPY-LI (6). Low IAT has previously been found to be associated with joint/muscle pain and tenderness (7). In a recent study the TMJ aspirate concentration of NPY-LI has also been found to be directly associated with pain in the joint (8). The effect of GC on the local release of NPY from nerve terminals involved in neurogenic inflammation in general, and in the synovial membrane in particular, is unknown. There is thus no information available on the

Table 1. Age, clinical variables, and mean temporomandibular joint (TMJ) concentration of neuropeptide Y-like immunoreactivity (NPY-LI) in six healthy individuals and ten TMJs

Variable	Mean	*n*	SD	Range Min	Range Max
Age, years	36	6	8	27	57
MVM*, mm	50.8	6	5.7	46	61
Pain threshold, N/cm^2	17.5	10	5.1	12.3	27.0
Pain tolerance, N/cm^2	38.7	10	6.8	29.4	49.1
TPM†	2.3	6	2.9	0	7
TPT‡	0.5	10	0.8	0	2
PM§	0.2	6	0.4	0	1
NPY-LI¶, pM	233	10	137	57	501

*MVM = maximal voluntary mouth opening capacity.
†TPM = number of masticatory muscles tender to digital palpation.
‡TPT = score of tenderness to lateral and posterior palpation of the TMJ.
§PM = number of painful mandibular movements.
¶NPY-LI = temporomandibular joint aspirate concentration of NPY-LI.

relationship between GC and NPY in peripheral tissues. The specific aim of this study was therefore to investigate the short-term effect of local administration of GC on joint fluid concentration of NPY in TMJ arthritis.

Materials and methods

Healthy individuals

Six individuals (10 TMJs), two men and four women, were included in the study as healthy controls with regard to the status of the TMJ and mandibular muscles and the TMJ fluid level of NPY-LI. They were subjectively symptom-free but were examined in the same manner as the patients (Table 1).

Patients

This study comprised 22 patients (29 TMJs), 19 women and 3 men with clinical signs and symptoms of TMJ arthritis—that is, local pain and tenderness to palpation of the joint. The mean age of the patients was 54 years. The patients were allocated by diagnosis into two groups: a specific inflammatory joint disease group (group I) and an unspecific inflammatory joint disease group (group II). Group I included 16 patients, 14 women and 2 men, of whom 9 had rheumatoid arthritis (7 RF+), 4 had ankylosing spondylitis, 1 had psoriatic arthritis, 1 had Sjögren's syndrome, and 1 had common variable immunodeficiency. Group II comprised 6 patients, 5 women and 1 man, of whom 2 had chronic unspecific polyarthritis, 2 had chronic unspecific monoarthritis, and 2 had fibromyalgia. The distribution of age and the duration of TMJ and general joint symptoms are shown in Table 2. The patients had not been subjected to any other recent treatment of the TMJ symptoms than with analgesics, which 12 of the patients (75%) in group I and 5 of the patients (83%) in group II had taken during the study.

Table 2. Age (years) and duration (years) of subjective symptoms from the temporomandibular joint (TMJ) and in general in patients with specific inflammatory joint disease (group I) and in those with unspecific inflammatory joint disease (group II) before intra-articular glucocorticoid treatment of the TMJ. Number of patients: group I, 16; group II, 6

	Group I				Group II			
			Range				Range	
Variable	Mean	SD	Min	Max	Mean	SD	Min	Max
Age	54.7	13.1	27	72	52.3	11.0	40	68
Duration								
TMJ	4.0	5.1	0.5	20	5.1	4.4	0.5	10
General	10.6	10.2	0	40	14.7	14.3	0	35

The study was approved by the local Ethical Committee at Huddinge Hospital (176/91).

Inclusion and exclusion criteria

The criteria for inclusion were 1) diagnosis of systemic or local inflammatory joint disease and 2) pain localized to the TMJ for a period of at least 6 weeks and tenderness to palpation of the joint laterally or posteriorly.

Patients whose symptoms could be referred to disease in other components of the craniomandibular system were excluded (for example, toothache, myalgia, neuralgia). Local infection of the skin over the TMJ or superficial masseter muscle was considered a contraindication for arthrocentesis.

Treatment and examination schedule

The patients were examined and, if the condition was in concordance with the inclusion criteria, given the injection at the first visit. The patients were re-examined at random either 2–3 weeks (median, 3 weeks; 14 patients) or 4–6 weeks later (median, 6 weeks; 8 patients).

Assessment of subjective symptoms and clinical signs

At each visit a 100-mm visual analogue scale (VAS) with end-points marked 'No pain' and 'Worst pain ever experienced' was used to assess the highest degree of pain during the last week. After the initial visit, the patients were also asked whether their symptoms were eliminated, improved, unchanged, or impaired as compared with visit 1 (subjective treatment effect (STR)).

Routine clinical examination methods were used, including examination for tenderness to palpation of the

TMJ (laterally and posteriorly) and masticatory muscle regions, maximum voluntary mouth opening (MVM), and pain on mandibular movement (PM). A tenderness to palpation score of the TMJ (TPT) was adopted which comprised 1–2 units each for tenderness of the lateral and posterior aspect of the joint on each side (0–4 units). Two units were scored if the palpation caused a pain reflex. The number of tender muscles causing pain reflexes (TPM) was counted. The pain threshold and pain tolerance threshold to pressure over the lateral aspect of the TMJ was assessed in N/cm^2 with an algometer (Pain Diagnostics and Thermography Co., USA).

Arthrocentesis

Local anesthesia of the TMJ was obtained by blocking the auriculotemporal nerve with 1.0–2.0 ml 2% lidocaine (Xylocain®) injected with a standard disposable needle (diameter, 0.4 mm). The TMJ was punctured with a standard disposable needle with a diameter of 0.65 mm and a length of 30 mm. The needle was inserted into the posterior part of the upper joint compartment.

Samples of joint fluid were aspirated with 1.0 ml saline, which was injected slowly and was aspirated after 20 sec. The aspirate volumes were measured, and the samples were thereafter diluted in 0.25 ml 5000 IE/ml heparin sodium (Heparin®) and 0.25 ml 10,000 KIE/ml aprotinin (Trasylol®), then immediately cold-centrifuged (800 *g* for 3 min) and frozen (−70°C).

Drug

The acetate ester of methylprednisolone (40 mg/ml) with added lidocaine hydrochloride (10 mg/ml) and sodium chloride (Depo-Medrol-Lidocaine®; Upjohn, USA) was used. A volume of 0.5–0.7 ml of the drug was injected into the upper joint compartment after diagnostic aspiration.

Radioimmunoassay (RIA)

The joint fluid was analyzed for neuropeptide-Y-like immunoreactivity (NPY-LI). Samples were extracted using a reverse-phase C18 cartridge (Sep Pak, Waters) and analyzed with a competitive radioimmunoassay (9–11).

NPY-LI was analyzed using antiserum N1, which cross-reacts 1.0% with avian pancreatic polypeptide but not with other peptides. Intra- and inter-assay coefficients of variation were 7% and 14%, respectively. The detection limit of NPY-LI with this radioimmunoassay was 8 pM.

Statistics

Differences between visits in subjective and clinical variables were measured at the ordinal level for STR, VAS, PM, TPM, and TPT and were tested for statistical significance with Wilcoxon's matched ranked test and for the other variables with Student's paired *t* test. Pearson's product-moment correlation coefficient and Spearman's ranked correlation coefficient (when at least one variable was measured at the ordinal level) were used to test the significance of correlations between changes in the different variables.

Results

The results of the GC treatment are shown in Table 3.

Differences between healthy individuals and patients

Before treatment the joint fluid concentration of NPY-LI in the healthy individuals and patients differed significantly in group I ($p < 0.01$) and in group II ($p < 0.05$). In both groups the pain threshold and pain tolerance threshold showed a significant difference compared with the healthy individuals (pain threshold: group I, $p < 0.01$; group II, $p < 0.05$; pain tolerance threshold: group I and group II, $p < 0.001$).

After treatment, there was no significant difference in joint fluid concentration of NPY-LI between group I and the healthy individuals at the 2- to 3-week follow-up, but a significant difference was found at the 4- to 6-week follow-up ($p < 0.01$). Two to 3 weeks after treatment there was also a significant difference between the patients in group I and the healthy individuals with regard to the pain tolerance threshold ($p < 0.001$). Four to 6 weeks after treatment there was a significant difference between the patients in group I and the healthy individuals with regard to the pain threshold ($p < 0.05$) and the pain tolerance threshold ($p < 0.001$).

Subjective symptoms

For group I the treatment resulted in improvement of the pain condition according to the patients' own evaluation of the treatment result (STR) both at the 2- to 3-week and at the 4- to 6-week follow-up visits ($p < 0.001$ and $p < 0.05$, respectively) (Fig. 1). The VAS scale showed a reduction of pain at both follow-up visits in this group ($p < 0.01$ and $p < 0.05$, respectively) (Fig. 2) but much less so at 4–6 weeks.

Clinical signs

The pain threshold to lateral pressure over the TMJ was increased after 2–3 weeks in group I ($p < 0.05$), as was the pain tolerance threshold ($p < 0.05$) (Fig. 3). PM was also decreased in group I 2–3 weeks after treatment ($p < 0.01$) (Fig. 3). These changes could not be found 4–6 weeks after treatment (Fig. 4).

Table 3. Neuropeptide Y-like immunoreactivity (NPY-LI) concentrations, subjective symptoms, and clinical signs before and after two separate follow-up intervals after a single intra-articular injection of glucocorticoid

	2–3 weeks					4–6 weeks				
		BT‡		AT‡			BT‡		AT‡	
Variable†	*n*	Mean	SD	Mean	SD	*n*	Mean	SD	Mean	SD
Group I										
NPY-LI, pM	11	1411	2665	896*	1231	10	1216	1225	1293	885
STR	8	3.0	0.0	1.5***	0.8	8	3.0	0	1.7*	1.2
VAS	8	5.9	2.8	3.3**	1.7	8	7.0	1	5.1*	2.3
MVM, mm	8	40.3	7.7	42.8	5.9	8	35.5	10.5	35.1	9
Pain threshold, N/cm^2	11	9.6	5.0	13.4*	7.4	10	12.0	5.1	10.1	6.0
Pain tolerance, N/cm^2	11	15.2	8.0	21.1	9.0	10	20.3	10.6	18.7	8.6
TPM	8	4.6	3.1	4.5	3.4	8	6.8	2.1	5.7	3.0
TPT	11	1.4	1.3	1.2	1.5	10	1.7	1.6	0.8	1.2
PM	8	4.1	0.7	2.4*	1.7	8	2.8	2.0	3.0	1.2
Group II										
NPY-LI, pM	6	1399	1486	801	623	2	540	345	584	28
STR	5	3.0	0.0	2.7	1.3	1	2.0	NA	2.0	NA
VAS	5	6.7	1.2	5.8	2.3	1	5.0	NA	3.0	NA
MVM, mm	5	31.2	8.4	36.4	3.6	1	35.0	NA	39.0	NA
Pain threshold, N/cm^2	6	10.2	8.1	11.5	8.5	2	11.8	2.2	11.1	1.8
Pain tolerance, N/cm^2	6	18.8	11.9	18.8	15.8	2	22.1	2.5	22.1	0.0
TPM	5	4.7	4.8	4.0	4.5	1	5.0	NA	4.0	NA
TPT	6	1.7	1.4	1.6	1.6	2	0.5	0.7	0.5	0.7
PM	5	4.0	1.7	3.2	1.2	1	4.0	NA	5.0	NA

Wilcoxon's matched test; significance levels: *$p < 0.05$; **$p < 0.01$; and ***$p < 0.001$. NA = not applicable.
†STR = subjective treatment result (0 = no remaining symptoms, 1 = much improved, 2 = slightly improved, 3 = no difference, 4 = slightly aggravated, and 5 = much aggravated symptoms compared with the pretreatment condition); VAS = visual analogue scale (0–10); MVM = maximal voluntary mouth opening; TPM = muscle tenderness to palpation; TPT = TMJ tenderness to palpation; PM = pain on movement of the mandible.
‡BT = before treatment, and AT = after treatment.

NPY-LI

The mean NPY-LI concentration of the patients in group I, who were re-examined 2–3 weeks after treatment was 1411 pM before and 896 pM after treatment. This decrease was statistically significant ($p < 0.05$). The mean NPY-LI concentration of patients in group I who were re-examined 4–6 weeks after treatment was 1216 pM before and 1293 pM after treatment. In Group II the corresponding values were 1399 pM before and 801 pM 2–3 weeks after and 540 pM before and 584 pM 4–6 weeks after treatment.

Correlation between treatment effects

There was a negative correlation between treatment effects on NPY-LI and pain tolerance threshold at the 4- to 6-week follow-up visit in group I ($r = -0.64$, $p = 0.05$).

NPY-LI as background factor

The reduction of NPY-LI 2–3 weeks after the GC injection was positively correlated to the pretreatment level of NPY-LI in group I ($r = 0.95$, $p < 0.001$) and group II ($r = 0.91$, $p < 0.05$). The reduction of NPY-LI after 4–6 weeks was also positively correlated to the pretreatment level of NPY-LI in group I ($r = 0.89$, $p < 0.001$).

In group I there was a positive correlation between the pretreatment level of NPY-LI and the treatment effect on pain tolerance threshold after 4–6 weeks ($r = 0.67$, $p < 0.05$).

Discussion

Significant improvement, including pain, pain threshold, pain tolerance threshold, and pain on mandibular movement, was found in group I, the specific inflammatory disease group. This result is not difficult to explain, since GC has a profound effect on inflammatory conditions. It is also in agreement with a previous study on RA in the TMJ (5). However, no significant improvement was found for mouth opening capacity. This finding might be explained by an intra-articular abnormality, with adherences between the condyle and temporal fossa, which is frequent in this disease group. Group II also showed an improvement of subjective symptoms and clinical signs, which, however, was not statistically significant and therefore not conclusive.

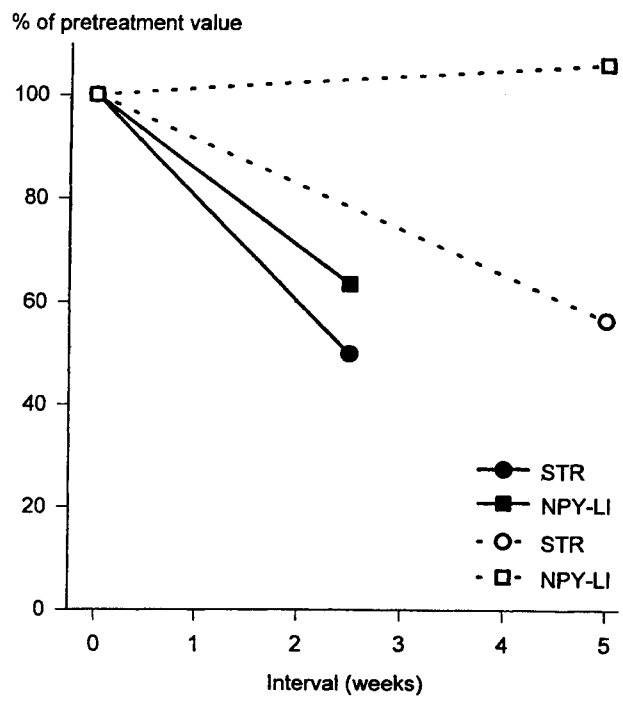

Fig. 1. Subjective treatment result (STR) and temporomandibular joint aspirate level of neuropeptide Y-like immunoreactivity (NPY-LI) (pM) in percentage of pretreatment values before treatment and at follow-up visits 2–3 weeks (11 patients) or 4–6 weeks (10 patients) after intra-articular glucocorticoid treatment in patients with specific inflammatory joint disease. Results at 2–3 weeks: STR, $p < 0.001$; NPY-LI, $p < 0.05$ and at 4–6 weeks: STR, $p < 0.01$; NPY-LI, NS.

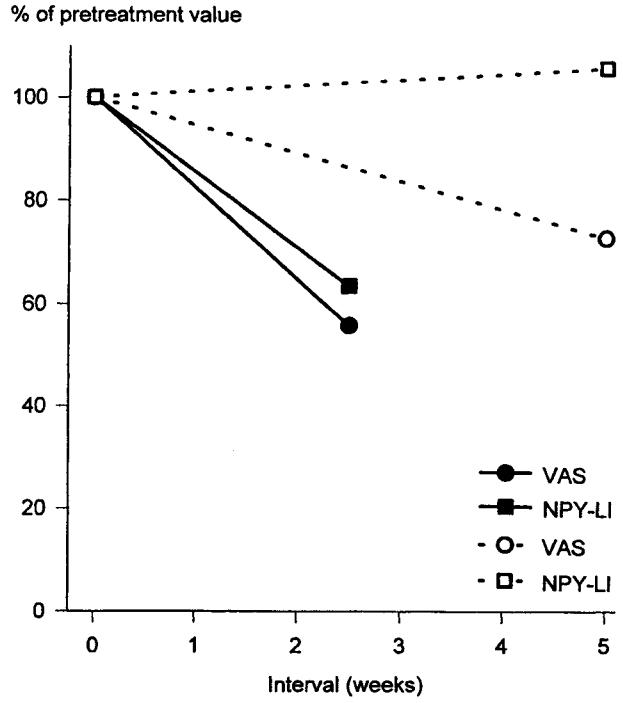

Fig. 2. Visual analogue scale (VAS) and temporomandibular joint aspirate level of NPY-LI (pM) in percentage of pretreatment values before and 2–3 (11 patients) or 4–6 weeks (10 patients) after intra-articular glucocorticoid injections in patients with specific inflammatory joint disease. Results at 2–3 weeks: VAS, $p < 0.01$; NPY-LI, $p < 0.05$ and at 4–6 weeks: VAS, $p < 0.05$; NPY-LI, NS). See legend to Fig. 1 for other abbreviations.

An increase in the pain threshold and pain tolerance threshold to lateral pressure on the joint, like the one found 2–3 weeks after treatment, was not found in the patients at the 4- to 6-week follow-up visit. This is in agreement with the known duration of the intra-articular pharmacodynamic effect of this particular GC (about 3–4 weeks). Since no treatment effect at all was detected for palpatory tenderness, the pain and pain tolerance thresholds to lateral pressure seem to have less variance and to be more sensitive indicators for assessment of joint tenderness than digital palpation.

The specific inflammatory joint disease group showed a significant decrease of the peptide level in the joint aspirates at the 2- to 3-week follow-up study, which may be due to decreased release from the nerve terminals or an increased local metabolism of the peptide. The findings in the unspecific inflammatory joint disease group indicate a similar decrease of the peptide level, which, however, was not statistically significant and therefore not conclusive in this study.

The synthetic steroid dexamethasone has been found to suppress the calcitonin gene-related peptide and substance P (SP) neuropeptide immunoreactivity in dental nerves of adult rats (12), but nothing has been reported about the peripheral influence on NPY. However, there is clinical evidence suggesting that the peripheral sympathetic nervous system contributes to arthritis in patients with reflex sympathetic dystrophy and that corticosteroids can reduce the inflammation associated with that disorder (13). An experimental study showed that intra-thecal administration of NPY produced a dose-dependent increase of the nociceptive threshold, as assessed by the hot-plate test, and that NPY and its fragments had analgesic potency (14). However, in the paw pressure test of the same study, NPY was not found to be anti-nociceptive, even at high doses. The physiologic mechanism behind this difference in action cannot be completely explained at present, but similar modality differences have been reported previously for other nervous transmittor systems. Our findings indicate that the presence of NPY-LI in the peripheral joint tissues is associated with a decrease of the nociceptive threshold in contrast to its reported effect in the central nervous system. In experimental adjuvant-induced arthritis in rats NPY played an important role as regulator of the severity of joint inflammation together with SP (15), and increased release from peripheral nerves of the sympathetic system

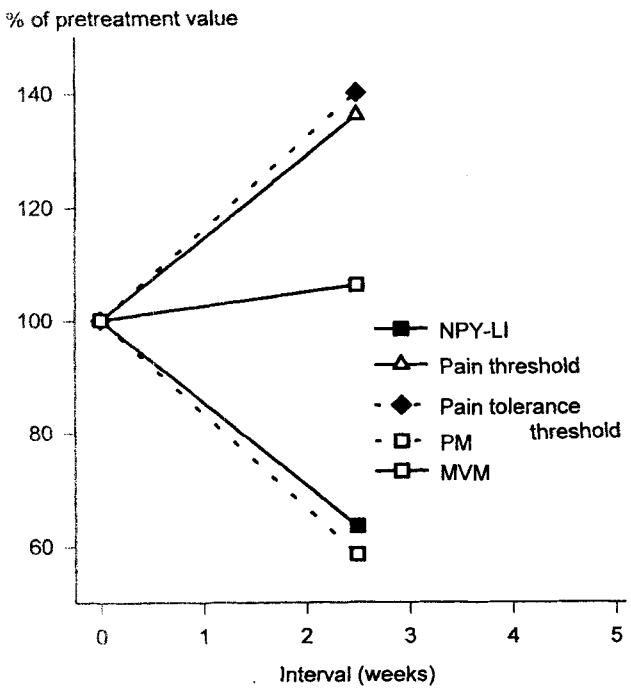

Fig. 3 Temporomandibular joint aspirate level of NPY-LI (pM) and clinical variables in percentage of pretreatment values before and 2–3 weeks after intra-articular glucocorticoid treatment in 8 patients/11 joints with specific inflammatory joint disease. PM = pain on mandibular movement; MVM = maximum voluntary mouth opening capacity (mm). See legend to Fig. 1 for other abbreviations.

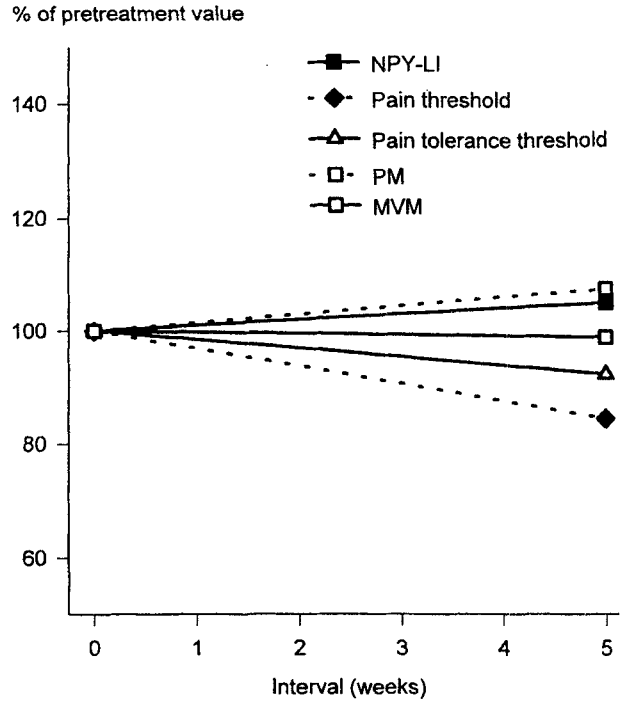

Fig. 4. Temporomandibular joint aspirate level of NPY-LI (pM) and clinical variables in percentage of pretreatment values before and 4–6 weeks after intra-articular glucocorticoid treatment in 8 patients/10 joints with specific inflammatory joint disease. PM = pain on mandibular movement; MVM = maximum voluntary mouth opening capacity (mm). See legend to Fig. 1 for other abbreviations.

has been associated with increases in joint inflammation and destruction (13). Our results are in agreement with these latter studies. In our study we observed a short-term decrease of TMJ aspirate concentration of NPY-LI in parallel with an improvement of the clinical variables in group I. This finding indicates that NPY-LI is involved as a mediator or modifier of joint pain and dysfunction. NPY-LI has also been found in high concentrations in the synovial fluid of patients with arthritis of the knee (16), which together with the results of this study suggests that this neuropeptide is involved in the regulation of inflammatory joint disease in humans.

In this study the short-term treatment effect of intra-articular GC was statistically significant in group I, the patients with specific inflammatory joint diseases, but not in the patients with unspecific joint diseases. The small number of patients in group II, however, precludes the possibility of any conclusion about the conditions in this patient category.

There was a negative correlation between the treatment effects on NPY-LI and pain tolerance threshold, which means that the decrease in NPY-LI was associated with an increased tolerance to lateral pressure over the joint. The pressure pain threshold indicators have been reported to be reliable for assessment of the degree of local tenderness in the jaw muscles (17). This study indicates that both the pressure pain threshold and the pressure pain tolerance threshold are useful indicators also for assessment of TMJ tenderness. It was remarkable that the subjective response to the treatment (STR) remained longer than the VAS response, the clinical variables, and the NPY-LI level, which means that the patients on direct questioning still reported an improvement of their condition at the 4- to 6-week follow-up visit, even though the clinical picture had deteriorated. This finding is probably due to a placebo effect or a delayed subjective response.

There was a positive correlation between the joint aspirate pretreatment level of NPY-LI and the reduction of NPY-LI 2–3 weeks after treatment in both patient groups; that is, a high level of NPY-LI before treatment was associated with greater reduction of the NPY-LI level after treatment than a low pretreatment level. After 4–6 weeks this relation could still be observed in group I. This finding is in agreement with the positive correlation found in group I between the pretreatment joint aspirate content of NPY-LI and the treatment effect on pain tolerance threshold; that is, the patients with high pretreatment joint aspirate level of NPY-LI obtained a greater increase of pain tolerance to lateral pressure over the TMJ after intra-articular

GC treatment than the patients with low pretreatment NPY-LI level.

The healthy individuals in this study were younger than the corresponding patients, but they were mainly female, like the patients. They were all subjectively symptom-free, although 4 of them had some muscle tenderness, and 2 of the 13 joints examined had slight palpatory tenderness. Owing to the considerable variation in NPY-LI level of the healthy individuals the normal range of intra-articular NPY-LI is quite large in this sample. However, the distribution of NPY-LI in group I was significantly different from that of the healthy individuals, as was the pain threshold and pain tolerance threshold. The persisting difference between the patients in group I and the healthy individuals in the pain tolerance threshold indicates that the patients were not completely recovered after treatment, even in the short term.

The results of this study show that intra-articular GC treatment causes a short-term decrease of the TMJ fluid level of NPY-LI in patients with specific inflammatory joint disease. At the same time the subjective symptoms and clinical signs improve. Our findings also indicate that decreased level of NPY-LI in the TMJ fluid is associated with an increase of the nociceptive threshold and that NPY-LI therefore is involved as a mediator or modifier of TMJ pain and dysfunction.

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References

1. Hollander JL. Arthritis and allied conditions. 7th ed. Philadelphia: Lea & Febiger, 1969:381–936.
2. Lacronique J, Russo-Marie F, Marsac J. Mechanism of action and effects of corticoids in asthma. Rev Mal Respir 1989;6:15–30.
3. Kopp, S, Wenneberg B. Effects of occlusal treatment and intra-articular injections on temporomandibular joint pain and dysfunction. Acta Odontol Scand 1981;39:87–96.
4. Kopp S, Carlsson GE, Haraldson T, Wenneberg B. Long-term effect of intra-articular injections of sodium hyaluronate and corticosteroid on temporomandibular joint arthritis. J Oral Maxillofac Surg 1987;45:929–35.
5. Kopp S, Akerman S, Nilner M. Short-term effects of intra-articular sodium hyaluronate, glucocorticoid, and saline injections on rheumatoid arthritis of the temporomandibular joint. J Craniomandib Disord 1991;5:231–8.
6. Appelgren A, Appelgren B, Kopp S, Lundeberg T, Theodorsson E. Relation between the intra-articular temperature of the temporomandibular joint and the presence of neuropeptide Y-like immunoreactivity in the joint fluid. A clinical study. Acta Odontol Scand 1993;51:1–8.
7. Åkerman S, Kopp S. Intra-articular and skin surface temperature of human temporomandibular joint. Scand J Dent Res 1987;95: 493–8.
8. Appelgren A, Appelgren B, Kopp S, Lundeberg T, Theodorsson E. The relationship between neuropeptides in arthritic temporomandibular joint and symptoms and signs from the stomatognatic system with special consideration to rheumatoid arthritis. J Orofacial Pain. In press.
9. Theodorsson-Norheim E, Brodin E, Norheim I, Rosell S. Antisera raised against eledoisin and kassinin detect immunoreactive material in rat tissue extracts: tissue distribution and chromatographic characterization. Regul Pept 1984;9:229–44.
10. Theodorsson-Norheim E, Hemsén A, Lundberg JM. Radioimmunoassay for neuropeptide Y (NPY): chromatographic characterization of immunoreactivity in plasma and tissue extracts. Scand J Clin Lab Invest 1985;45:355–65.
11. Theodorsson-Norheim E, Hemsén A, Brodin E, Lundberg JM. Sample handling techniques when analyzing regulatory peptides. Life Sci 1987;41:845–8.
12. Hong D, Byers MR, Oswald RJ. Dexamethasone treatment reduces sensory neuropeptides and nerve sprouting reactions in injured teeth. Pain 1993;55:171–81.
13. Levine JD, Dardick SJ, Roizen MF, Helms C, Basbaum AI. Contribution of sensory afferents and sympathetic efferents to joint injury in experimental arthritis. J Neurosci 1986;6:3423–9.
14. Hua XY, Boublik JH, Spicer MA, Rivier JE, Brown MR, Yaksh TL. The antinociceptive effects of spinally administered neuropeptide Y in the rat: systematic studies on structure-activity relationship. J Pharmacol Exp Ther 1991;258:243–8.
15. Hope PJ, Jarrott B, Schaible HG, Clarke RW, Duggan AW. Release and spread of immunoreactive neurokinin A in the cat spinal cord in a model of acute arthritis. Brain Res 1990;533:292–9.
16. Larsson J, Ekblom A, Henriksson K, Lundeberg T, Theodorsson E. Immunoreactive tachykinins, calcitonin gene-related peptide and neuropeptide Y in human synovial fluid from inflamed knee joints. Neurosci Lett 1989;100:326–30.
17. List T, Helkimo M, Falk G. Reliability and validity of a pressure threshold meter in recording tenderness in the masseter muscle and the anterior temporalis muscle. Cranio 1989;7:223–9.

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