Effect of local glucocorticoid injection on masseter muscle level of serotonin in patients with chronic myalgia

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The aim of this study was to compare the effects on the level of serotonin (5-HT) in the masseter muscle by intramuscular glucocorticoid (GC) administration in patients with fibromyalgia (FM) and localized myalgia (LM), as well as to determine associated changes in pain, tenderness, and microcirculation. The study comprised 22 patients with pain and tenderness in the masseter muscle region. Ten patients (all women) had FM, and 12 (1 man and 11 women) had LM involving the temporomandibular system. The patients were examined clinically and by microdialysis at 2 visits 2–3 weeks apart and received local glucocorticoid treatment at the first visit. The ratio (S1/S2) between the initial level of 5-HT (S1) and steady state level (S2) was used as a relative measure of the intramuscular release of 5-HT. This ratio decreased significantly after treatment in the FM group. In the FM group there was also a negative correlation regarding changes between visits of 5-HT and changes of intramuscular temperature. In the LM group there was a negative correlation regarding changes between visits of 5-HT and changes of pressure pain threshold and pressure pain tolerance level. This study indicates that there is a reduction of the ratio between initial 5-HT and steady state level in the painful masseter muscle after intramuscular GC administration to FM patients, a reduction not present in the LM patients. In addition, 5-HT seems to be involved in the modulation of local muscle microcirculation in FM patients and in hyperalgesia in LM patients. □ *Fibromyalgia; localized myalgia; pain*

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Patients with temporomandibular disorders often complain of local masticatory muscle pain (LM), and when examined these muscles often show various degrees of tenderness to palpation. Patients with fibromyalgia (FM), characterized by widespread pain and tenderness to palpation (1), also often show pain and tenderness of the masticatory muscles (2). In both conditions neither the etiology nor the pathophysiology of the muscle pain and tenderness is known in sufficient detail to allow a rational treatment regimen.

It has been suggested that an inflammatory process due to mechanical microtrauma causes local muscle pain (3). In experimental studies, biopsies from painful muscles have presented pathological changes such as mast cell degranulation, which may initiate an inflammatory response (4). The number of mast cells in skin biopsies from FM patients has been found to be increased compared with those from healthy controls (5). These findings together indicate that mast cells are of importance in the pathophysiology of FM (6). Furthermore, Henriksson & Bengtsson (7) have proposed that sensitization of muscle nociceptors due to disturbances of the microcirculation may be of importance for FM. Substances that are released after tissue trauma and may sensitize muscle nociceptors include mediators such as serotonin, bradykinin, and prostaglandins (8).

Serotonin (5-HT) is released from blood platelets as a result of tissue damage (9) and from mast cells (10). It is a strong mediator of pain (11) as well as hyperalgesia (12). It has been found to participate in the mediation of pain from inflamed tissues by exciting and sensitizing fine primary afferent units (13). In a previous study we found a higher level of 5-HT in the masseter muscle after local tissue trauma in patients with FM and LM than in healthy subjects. This may be due to a condition in which patients with FM and LM are hyperreactive to trauma of muscle tissue with respect to 5-HT release (14). There was also an association between pain as well as hyperalgesia and the level of 5-HT in the masseter muscle, suggesting that 5-HT is involved in the development or modulation of muscular pain. It is known to be involved in the regulation of tissue blood flow (15) by constricting larger arterial vessels and dilating smaller pre-capillary arterioles (16). FM patients show significantly lower intramuscular temperatures than healthy subjects, indicating a disturbed microcirculation (17).

Treatment with intramuscular injections of glucocorticoid (GC) in combination with local anesthetic has proved to be beneficial for patients with myofascial pain (18). GC exerts an anti-inflammatory effect by blocking the synthesis of prostaglandins and leukotrienes (19) and by inhibiting the production of interleukin 1β. GC has furthermore been reported to inhibit the release of 5-HT from basophilic granulocytes through a mechanism independent of phospholipase A2 (20). However, the inhibition of arachidonic acid release by GC was found to be more

potent than the inhibition of 5-HT release. The pain relief that has been reported after local GC treatment in myofascial pain conditions could be due to one or more of these anti-inflammatory effects or to a placebo effect.

The response to local GC injections into the painful masseter muscle of patients with FM and LM has been found to differ in some important respects (21). Since previous results indicate that patients with FM and LM differ from healthy subjects with respect to intramuscular 5-HT release (14), it would be interesting to study if there is a different effect on 5-HT of local GC administration to these patients. Our hypothesis was that the effects of local GC administration differ between patients with FM and LM as regards 5-HT release. The first aim of this study was therefore to investigate and compare the changes following local GC administration regarding the level of 5-HT in the masseter muscle in patients with FM and LM of the temporomandibular system. A second aim was to determine associated changes regarding pain, tenderness, and microcirculation.

Table 1. Age (years), sex, and duration (years) of general and local symptoms in 10 patients with fibromyalgia (FM) and 12 patients with localized myalgia (LM) of the temporomandibular system

FM					LM			
			Duration					Duration
Patient	Age	Sex	General	Local	Patient	Age	Sex	Local
A	42	F	2	10	K	32	F	13
B	73	F	12	13	L	74	F	10
C	33	F	25	10	M	48	F	6
D	56	F	25	25	N	44	M	3
E	44	F	8	10	O	38	F	7
F	36	F	2	15	P	27	F	2
G	34	F	3	10	Q	44	F	15
H	64	F	17	14	R	72	F	23
I	43	F	6	2	S	43	F	8
J	42	F	13	17	T	33	F	5
					U	43	F	9
					V	28	F	3
Mean	47		11	13		44		9
s	13		9	6		15		6
$s_{\bar{x}}$	4		3	2		4		2

Materials and methods

Patients

The study comprised 22 patients, 1 man and 21 women, attending the Clinic of Oral Physiology, Karolinska Institute. The distribution of age, sex, and duration of disease is shown in Table 1. Ten patients had FM and 12 had LM in the temporomandibular system. Inclusion criteria were pain in the masseter muscle region for more than 3 months and tenderness to digital palpation of at least 1 of the 2 superficial masseter muscles. For patients included in the FM group, a diagnosis of FM according to the criteria by the American College of Rheumatology (1) was also required. The diagnosis of FM was made by the patient's physician. Exclusion criteria were symptoms that could be referred to disease in other components of the temporomandibular system (e.g. toothache, neuralgia, local temporomandibular joint disease) and local skin infection over the injection site. All examinations were performed in the morning and by the same investigator (P. Alstergren, M. Ernberg, B. Hedenberg-Magnusson) on both occasions with a 2- to 3-week interval.

Two of the patients in the FM group were on medication with antidepressants and 2 with analgesics. In the LM group 1 patient medicated with antidepressants and 3 with analgesics. The medication did not change between visits for any patient.

The selection of patients and the methods used were approved by the local ethics committee at Huddinge Hospital, Karolinska Institute, Stockholm.

Methods

Assessment of pain. The same protocol was used at both visits. A 100-mm visual analog scale (VAS, Pharmacia-Upjohn, Stockholm, Sweden), with endpoints marked as 'No pain' and 'Worst pain ever experienced', was used to assess the worst degree of pain during the last week.

Clinical examination. A routine clinical examination of the temporomandibular system was performed, including examination for tenderness to palpation of masticatory muscle regions (22). A 4-point scale was used: 0 = no tenderness, 1 = mild tenderness, 2 = moderate tenderness with palpebral reflex, 3 = marked tenderness with a defense withdrawal reflex. The most tender point of the superficial masseter muscle and the corresponding point on the contralateral side were recorded on a schematic figure and used in all further investigations concerning the masseter muscle. A pressure algometer with a blunt recording tip of 10 mm in diameter (Pain Diagnostics and Thermography Co., Great Neck, N.Y., USA) was used to assess the pressure pain threshold (PPT) and pressure pain tolerance level (PPTL) of the masseter muscle. The pressure rate used was 50 kPa s, and the patients were instructed to tell when the sensation of pressure changed to pain (PPT) and, in a different recording, when the pain became intolerable (PPTL).

Muscle puncture. Five minutes after skin-surface anesthesia with 1.0 mL lidocaine (Xylocain®, 20 mg/mL, Astra, Södertälje, Sweden), the masseter muscle was punctured with a standard catheter (diameter 1.2 mm; Venflon 2, Boc Ohmeda, Helsingborg, Sweden) to a depth of 20 mm from the entrance on the skin surface. The puncture was made at an angle of 45°, which left the catheter at a depth of 15 mm beneath the skin surface. The needle was thereafter withdrawn and the catheter pulled back 10 mm, leaving the catheter at a depth of 10 mm from the entrance on the skin surface and 7 mm beneath the skin surface. Finally, the catheter was cut 9 mm outside the skin surface.

Temperature recordings. The intramuscular temperature (IMT) of the masseter muscle was measured to estimate changes in the local microcirculation. The temperature was measured with a sterile thermocouple probe (diameter 0.7 mm; C-N7, Exacon Scientific Instruments APS, Roskilde, Denmark) that was inserted through the standard catheter to a depth of 20 mm from the entrance on the skin surface and 15 mm beneath the skin surface. The temperature was recorded by a digital thermometer (MC 9200, Exacon Scientific Instruments APS, Roskilde, Denmark) operating with an accuracy of 0.1°C. The recording was made when the temperature had been stable for 15 s.

Blood sampling. A venous blood sample of 2 mL was collected just before the microdialysis for analysis of 5-HT in blood serum (S-5-HT) at both visits, and the patients were therefore asked to avoid tryptophan-rich food (e.g. banana, pineapple, tomato) for 24 h before the examination.

Microdialysis. Intramuscular microdialysis was used to monitor the changes in 5-HT in the masseter muscle (M-5-HT). The patients were in either an upright or a supine position in a conventional dental chair, and they were instructed to avoid mandibular muscle activity (e.g. talking, chewing) in order not to interfere with the dialysis. The probe used for dialysis (CMA/10, Carnegie Medicine, Stockholm, Sweden) had a length of 30 mm and an outer diameter of 0.65 mm. It was inserted through the standard catheter to a depth of 20 mm from the entrance on the skin surface and 15 mm beneath the skin surface. The probe membrane, with a length of 10 mm and a diameter of 0.50 mm, was made of polycarbonate with a cut-off of 20 kDa. A microinfusion pump (CMA/100, Carnegie Medicine, Stockholm, Sweden) perfused the probe with 0.9% saline (Sodium Chloride, Pharmacia AB, Stockholm, Sweden) at a flow rate of 7 μL/min. This flow rate was chosen to obtain a sufficient volume of dialysate during a time period tolerable for the patient. During an initial stabilization period of 20 min, 140 μL dialysate was sampled (S1). The microdialysis was then continued for another 35 min (steady state) with sampling of another 250 μL dialysate (S2). The same probes were used at both visits and were put in alcohol and perfused with sterile water after the dialysis. The probes were then put in a tube with sterile water, capped, and stored in a refrigerator until the second visit. The dialysate samples were collected in capped polystyrene tubes that were kept on ice and shaded for light exposure by aluminum foil during the dialysis. After the dialysis, the dialysate samples were immediately frozen (−22°C).

Recovery test. An in vitro test of the recovery of 5-HT was performed in 18 probes that were placed in a solution of 5-HT (60 nmol/L) and perfused as described above. After a stabilization period of 30 min, 140 μL dialysate was sampled. The mean ($\pm$ $s_{\bar{x}}$) recovery was found to be $26 \pm 0.9\%$. To avoid any influence of the variability in recovery between different probes, the ratio between S1 and S2 was used as a relative measure of M-5-HT release. The ratios in dialysate levels between visits (i.e. S1 after/S1 before, and S2 after/S2 before treatment) were used in the correlation analysis.

Treatment

Injection of 0.3 ml methylprednisolone (Depo-Medrol®, 40 mg/mL, Upjohn, Kalamazoo, Mich., USA) was performed into the most tender part of the superficial masseter muscles after microdialysis at visit 1. The drug was given bilaterally (20 patients) or unilaterally (2 patients), depending on the presence of pain.

Biochemical analysis

The 5-HT samples were analyzed by a commercial enzyme immunoassay kit (Immunotech International, Marseille, France) with a detection limit of 0.5 nmol/L. According to the manufacturer, the intra- and interassay coefficients of variation vary from 7.9% to 9.4% and 6.2% to 9.9%, respectively. Values below the detection limit were considered as 0.5 nmol/L.

Statistics

Intraindividual differences between visits in M-5-HT levels were tested for statistical significance by the Wilcoxon signed-ranks test; intraindividual differences in S-5-HT level, by Student's paired *t* test. Differences between groups regarding changes between visits in M-5-HT levels (S1/S2, ratio after/before) were tested for statistical significance by the Mann–Whitney U-test; differences between groups regarding changes between visits in S-5-HT level (ratio after/before), by Student's unpaired *t* test. Correlations between changes in M-5-HT levels and changes of the other investigated variables were tested by Spearman's rank correlation coefficient. All tests were two-tailed. The value of the most tender superficial masseter muscle was used in the analysis, since some patients presented pain on one side only. The exact *P* values are presented; the level of significance was set to $P < 0.05$.

Results

The levels of M-5-HT as well as S-5-HT before and after GC treatment are shown in Table 2. In both groups there was a marked difference between S1 and S2 before as well as after treatment (FM: $P = 0.008$ and 0.058; LM: $P = 0.041$ and 0.050). This difference is reflected by the ratio S1/S2 before and after treatment. The ratio was reduced after treatment in both groups, but significantly only in the FM group ($P = 0.047$). The S-5-HT level showed a great variation in both groups, but did not change significantly between visits, either within groups (FM: $P = 0.365$ and LM: $P = 0.287$) or between groups ($P = 0.265$).

Table 2. Dialysate levels (ratio S1/S2) of serotonin (M-5-HT; nmol/l) in the most tender superficial masseter muscle as well as serum levels of 5-HT (S-5-HT; nmol/l) from patients with fibromyalgia (FM) and localized myalgia (LM) of the temporomandibular system before and after local glucocorticoid administration

FM					LM				
	M-5-HT S1/S2		S-5-HT			M-5-HT S1/S2		S-5-HT	
Patient	Before	After	Before	After	Patient	Before	After	Before	After
A	3.1	5.8	960	1460	K	5.7	7.4	500	360
B	2.4	1.0	150	1380	L	7.6	8.4	1040	600
C	6.8	4.3	800	1300	M	3.0	1.4	md	md
D	1.0	0.7	36	1640	N	14.8	8.8	880	820
E	5.9	2.2	1740	1020	O	2.0	1.3	md	md
F	4.2	3.9	md	md	P	3.8	1.8	1400	1440
G	5.0	3.2	700	md	Q	0.2	0.8	240	92
H	3.0	2.6	760	480	R	1.1	1.0	78	82
I	13.8	0.3	1380	980	S	0.3	0.6	800	900
J	8.6	8.4	520	340	T	2.2	6.8	900	1080
					U	7.1	0.4	420	400
					V	1.2	7.8	410	300
Median	4.6	2.9	Mean 783	1075	Median	2.6	1.6	Mean 667	607
IQR	2.9–7.3	0.9–4.6	$s_{\bar{x}}$ 204	165	IQR	1.1–6.8	0.9–7.7	$s_{\bar{x}}$ 128	141
n	10	10	*n* 9	8	*n*	12	12	*n* 10	10

S1 = dialysate sample 1, S2 = dialysate sample 2. IQR = interquartile range, *n* = number of observations, md = missing data. Significant difference regarding M-5-HT S1/S2 in the FM group between visits ($P = 0.047$).

Correlations between changes in levels of M-5-HT and changes in clinical variables between visits are shown in Table 3. There was no correlation between changes in M-5-HT level between visits and the background factors age and duration of disease in any group.

Discussion

The distribution of age and sex was similar in the two groups. The patients with FM showed a longer duration of local symptoms than the LM patients. However, the difference was not significant, and we therefore assume that the groups are comparable.

The M-5-HT levels reported in the present study are the dialysate levels and not the tissue levels. The latter would be much higher than the dialysate levels, owing to a non-total recovery of 5-HT by the microdialysis probes. To estimate the tissue level of a certain substance, an in vivo recovery test has to be performed. There are different methods described in the literature for such tests (23), but since they all are very time-consuming, we do not consider them applicable for clinical use. However, the in vitro variability of the recovery between probes was very low. To avoid comparison of dialysate levels between individuals or groups, we have used a ratio between initial and steady state dialysate samples (S1/S2). This ratio also eliminates the effects of 5-HT release due to unintended bleeding during the microdialysis. In the correlation analysis between changes in M-5-HT levels and changes

Table 3. Correlation between changes after treatment (ratio after/before) in dialysate levels of serotonin (5-HT) from the most tender superficial masseter muscle and clinical variables in patients with fibromyalgia (FM) and localized myalgia (LM) of the temporomandibular system. Statistically significant values denoted by bold figures

	FM				LM			
	VAS	PPT	PPTL	IMT	VAS	PPT	PPTL	IMT
5-HT S1 a/b								
r_s	0.11	0.63	**0.70**	**−0.73**	0.54	−0.24	−0.06	−0.08
n	8	10	**10**	**10**	12	12	12	12
P	0.800	0.052	**0.024**	**0.016**	0.072	0.448	0.848	0.816
5-HT S2 a/b								
r_s	0.20	0.62	0.61	**−0.70**	−0.01	**−0.77**	**−0.58**	−0.25
n	8	10	10	**10**	12	**12**	**12**	12
P	0.628	0.054	0.060	**0.024**	0.964	**0.003**	**0.048**	0.432

r_s = Spearman's rank correlation coefficient, *n* = number of muscles, $P = P$ value. S1 = dialysate sample 1, S2 = dialysate sample 2, VAS = pain assessed with a visual analog scale, PPT = pressure pain threshold, PPTL = pressure pain tolerance level, IMT = intramuscular temperature.

in clinical variables, we used a ratio between 5-HT levels before and after treatment (sample after/sample before) and used the same probe at both visits.

In an earlier study we compared the effects on subjective symptoms and clinical signs of intramuscular GC administration to patients with FM and LM (21). The present study aimed at comparing the effects on the level of 5-HT in the masseter muscle of intramuscular GC administration and associated changes of local pain and tenderness as well as intramuscular temperature. The previous study showed that there is a positive treatment effect on tenderness to digital palpation of the masseter muscle in both patient groups, but that only patients with LM experienced a subjective treatment effect according to their own evaluation and a reduction of the pain assessed with a VAS (14).

In both groups of the present study, there was a difference of 5-HT between S1 and S2 before treatment. The higher level in S1 is probably partly due to microbleeding from the trauma of the insertion of the catheter, but also to locally increased release of 5-HT from sources other than blood. This condition has been reported in a previous study of M-5-HT level in the masseter muscle of patients with FM and LM, as well as a control group of healthy subjects (14). In that study S1 was found to be higher in FM and LM patients than in healthy subjects. The ratio S1/S2 in the present study decreased significantly between visits in the FM group, indicating a reduced reactivity of the tissue to puncture trauma, which was not observed in the LM group. However, further investigation will be required to determine whether this is specifically due to the GC treatment or other mechanisms. The decrease in the ratio S1/S2 2–3 weeks after GC administration was close to the 5% significance level, which has to be interpreted in relation to the relatively small number of patients.

The serum level of 5-HT showed a great variation in both groups at both visits. This is difficult to explain with certainty, but it could be due to biological variation. The same methods were used for all patients, and according to the manufacturer the variations between enzyme immunoassay kits are quite small. A diurnal variation in S-5-HT has been reported (24), but since all blood samples were collected in the morning (at 0900 h), it is unlikely that this factor had any influence. There was no significant change in S-5-HT after treatment. It is unlikely that this local GC administration would have any significant systemic effect on the serum level of 5-HT, although local GC administration results in detectable amounts of the drug in the systemic circulation (25).

An interesting finding in the FM group was that decreased levels of masseter muscle 5-HT after treatment were associated with increased IMT. It has been reported that patients with FM show a decreased IMT (17), supporting the theory of a reduced microcirculation in FM patients (7). Thus, according to this study it is possible that intramuscular release of 5-HT in FM results in vasoconstriction of arteries, which in turn leads to ischemia. This may occur either directly via the 5-HT2 receptor or indirectly via the release of other vasoconstrictors, such as noradrenalin and neuropeptide Y (26). In the LM group there was an association between decrease of 5-HT levels and increase of PPT and PPTL, which indicates that peripheral 5-HT may play a role in the development or modulation of muscle hyperalgesia in this patient group. It has also been suggested that a prolonged sensitization of muscle nociceptors may cause secondary hyperalgesia due to central mechanisms (27), such as irreversible changes in second order sensory neurons. Therefore, a possible explanation of the decrease of local muscle hyperalgesia in LM might be decreased levels of 5-HT as well as other mediators (e.g. bradykinin, prostaglandins), which are no longer available in sufficient concentrations to sensitize nociceptors. As a result the pain threshold and pain tolerance level increase, and no pain response occurs after normal, non-nociceptive mechanical stimulation such as palpation of the muscle. In the FM group decreased levels of M-5-HT were associated with decreased PPTL, a finding that we cannot explain at present.

There were no strongly significant changes in M-5-HT 2–3 weeks after local GC administration, but the small number of patients should be taken into account. The reductions of pain and hyperalgesia that have been reported previously in these patient groups after GC administration (21) might therefore be due partly to prostaglandin synthesis inhibition or inhibition of mediators other than 5-HT. However, in the previous study no treatment effect at all could be found in the FM patients regarding spontaneous pain, which suggests mechanisms other than the arachidonic acid system (14).

In conclusion, this study indicates that there is a reduction of the ratio between initial 5-HT and steady state level in the painful masseter muscle after intramuscular GC administration to FM patients, a reduction not present in the LM patients. In addition, 5-HT seems to be involved in the modulation of local muscle microcirculation in FM patients and hyperalgesia in LM patients.

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