# Effect on prostaglandin $E_2$ and leukotriene $B_4$ levels by local administration of glucocorticoid in human masseter muscle myalgia

Britt Hedenberg-Magnusson, Malin Ernberg, Per Alstergren and Sigvard Kopp
Clinical Oral Physiology, Institute of Odontology, Karolinska Institutet, Huddinge, Sweden

Hedenberg-Magnusson B, Ernberg M, Alstergren P, Kopp S. Effect of prostaglandin $E_2$ and leukotriene $B_4$ levels by local administration of glucocorticoid in human masseter muscle myalgia. Acta Odontol Scand 2002;60:29–36. Oslo. ISSN 0001-6357.

Our aim was to determine whether masseter muscle (M) and plasma (P) levels of prostaglandin $E_2$ ($PGE_2$) or leukotriene $B_4$ ($LTB_4$) are influenced by local glucocorticoid administration and whether such changes would be associated with corresponding changes in local pain or hyperalgesia. Eighteen patients with fibromyalgia and 15 with local masseter myalgia were examined immediately before and 2 weeks after intramuscular administration of glucocorticoid with regard to masseter muscle resting pain and tenderness to palpation, pressure pain threshold, maximum voluntary mouth opening (MVM), and pain on maximum voluntary mouth opening. The primary criteria for inclusion were presence of pain for a period of at least 3 months and tenderness to digital palpation in the masseter muscle region. At both visits microdialysis samples were obtained from the masseter muscle, and venous blood was collected for analysis of $PGE_2$ and $LTB_4$. Dialysate levels of M-$PGE_2$ did not change significantly after glucocorticoid administration, but reduction of masseter resting pain and increase of MVM were associated with decrease of M-$PGE_2$ in the patients with fibromyalgia. Dialysate levels of M-$LTB_4$ increased in both groups. In the patients with local myalgia the plasma level of $LTB_4$ also increased, and this increase was associated with a decrease of pain and masseter tenderness. In conclusion, this study shows that reduction of masseter level of $PGE_2$ after intramuscular glucocorticoid administration is associated with a decrease of resting pain in patients with fibromyalgia. In addition, the masseter muscle level of $LTB_4$ increases in patients with fibromyalgia and local myalgia. □ *Glucocorticoid; leukotriene $B_4$; microdialysis; myalgia; prostaglandin $E_2$*

*Britt Hedenberg-Magnusson, Clinical Oral Physiology, Institute of Odontology, Karolinska Institutet, Box 4064, SE-141 04 Huddinge, Sweden. Tel: +46 8 728 82 29, fax: +46 8 608 08 81, e-mail: britt.hedenberg-magnusson@ofa.ki.se*

The pathophysiological mechanisms behind muscle pain are largely unknown, and treatment is accordingly unspecific. Skeletal muscle pain is mediated by $A_\delta$ fibers and C fibers. Both these afferents can be excited by chemical agents released on inflammation, such as bradykinin, prostaglandins, serotonin, and histamine (1), whereas C fibers also can be sensitized by these agents. During inflammation the proinflammatory mediators prostaglandin $E_2$ ($PGE_2$) and leukotriene $B_4$ ($LTB_4$) are released locally (2). $PGE_2$ is also released as a result of tissue damage (2) or hard exercise (3). Such trauma causes release of the enzyme phospholipase $A_2$, which in turn causes a breakdown of phospholipids in the cell wall to arachidonic acid, some of which is further transformed to prostaglandins by the enzyme cyclooxygenase (4, 5). The endomysium of the arterioles appears to be a major source of $PGE_2$ in mature skeletal muscle (6). It is at present unknown whether $PGE_2$ has any significant function in the development and maintenance of chronic muscular pain. With regard to $LTB_4$, arachidonic acid is metabolized to leukotrienes by the enzyme 5-lipoxygenase and released by leukocytes during inflammation. The enzyme 5-lipoxygenase has been found in rather few cell types, such as polymorphonuclear (PMN) cells, monocytes, macrophages, and mast cells. $LTB_4$ is a potent chemotactic agent causing adherence of neutrophils to the endothelial cells and stimulates release of lysosomal enzymes (7, 8). $LTB_4$ also induces chemotaxis, degranulation of PMN cells, allergic reactions, and sensitization of peripheral nociceptors (7, 9–11). In a recent study of masseter muscle myalgia, resting pain was found to be associated with the intramuscular level of $PGE_2$ in patients with general myalgia—that is, fibromyalgia according to the American College of Rheumatology (12). That study also showed that the level of $LTB_4$ was higher in the masseter muscle of patients with fibromyalgia than in patients with local myalgia (myofascial pain) of the temporomandibular system. $PGE_2$ and $LTB_4$ thus seem to play a role in the modulation of chronic muscle pain in fibromyalgia.

Glucocorticoids have an anti-inflammatory effect by inhibiting the activity of phospholipase $A_2$ (13) and thus block the synthesis of both prostaglandins and leukotrienes (14). Since $PGE_2$ and $LTB_4$ are produced in the masseter muscle of patients with both pain conditions, intramuscular administration of glucocorticoid might be expected to influence the pain in both patient groups. Systemic treatment of fibromyalgia patients with glucocorticoids has so far not shown convincing pain-relieving effects (15), whereas local intramuscular injections of glucocorticoid have been shown to decrease muscle tenderness to palpation both in fibromyalgia and localized myalgia and to decrease resting pain and to provide subjective improvement in patients with local myalgia (16).

The aim of this study was to determine whether intramuscular and plasma levels of $PGE_2$ or $LTB_4$ are influenced by local glucocorticoid administration and

Table 1. Variables related to the individual in 18 patients with fibromyalgia and 15 patients with local myalgia in the masseter muscle, before and after local glucocorticoid administration

| | Before treatment | | | After treatment | | | |
|---|---|---|---|---|---|---|---|
| | M | IQR | *n* | M | IQR | *n* | *P* |
| Fibromyalgia | | | | | | | |
| Age | 54 | 20 | 18 | | | | |
| Sex (F/M) | 16/2 | | | | | | |
| Duration | | | | | | | |
| Local | 13 | 11 | 18 | | | | |
| General | 14 | 10 | 18 | | | | |
| MVM | 47 | 12 | 18 | 49 | 12 | 18 | * |
| P-$PGE_2$ | 3 | 1 | 14 | 3 | 2 | 16 | |
| P-$LTB_4$ | 0 | 0 | 16 | 0 | 16 | 15 | |
| ESR | 11 | 12 | 14 | 11 | 8 | 11 | |
| CRP | 0 | 0 | 14 | 2 | 5 | 11 | |
| Local myalgia | | | | | | | |
| Age | 59 | 10 | 15 | | | | |
| Sex (F/M) | 12/3 | | 15 | | | | |
| Duration, local | 8 | 7 | 15 | | | | |
| MVM | 45 | 10 | 15 | 46 | 9 | 15 | |
| P-$PGE_2$ | 4 | 4 | 15 | 5 | 8 | 14 | |
| P-$LTB_4$ | 7 | 21 | 12 | 16 | 32 | 12 | * |
| ESR | 5 | 5 | 13 | 6 | 5 | 11 | |
| CRP | 0 | 0 | 13 | 1 | 0 | 11 | |

Age = age in years; Duration = duration of pain in years (local = masseter muscle region, general = generalized pain), M = median, IQR = interquartile range, *n* = number of observations, MVM = maximum voluntary mouth opening (mm), P-$PGE_2$ = plasma level of prostaglandin $E_2$ (pg/mL), P-$LTB_4$ = plasma level of leukotriene $B_4$ (pg/mL), ESR = erythrocyte sedimentation rate (mm/h), CRP = C-reactive protein (mg/L). *P* values for the difference before and after treatment are denoted by * for $P < 0.05$.

whether such changes are associated with corresponding changes in local pain and hyperalgesia.

## Materials and methods

### *Selection of patients*

Two patient groups were examined; 1 group included 18 patients with fibromyalgia in accordance with the American College of Rheumatology (ACR) criteria (17), and another group 15 patients with localized myalgia—that is, myofascial pain of the temporomandibular system in accordance with the definition of the American Association of Orofacial Pain (Table 1) (18). In both groups the primary criteria for inclusion were presence of pain in the masseter muscle region for a period of at least 3 months and tenderness to digital palpation of the masseter muscle. Patients with systemic inflammatory connective tissue diseases, arthrosis of the temporomandibular joint (TMJ), muscle pain due to external trauma, or symptoms that could be referred to disease in other components of the temporomandibular system were excluded (for example, toothache, neuralgia). Infection of the skin over the muscle was considered a contraindication for microdialysis and glucocorticoid administration by local injection. The patients had not been subjected to any other treatment of the local muscle pain than analgetics during the past month. All patients were instructed not to use any non-steroid anti-inflammatory drug within 24 h before the examinations.

The methods used and the selection of patients were approved by the local ethical committee at Huddinge Hospital, Karolinska Institutet, Huddinge, Sweden (151/93). The patients were informed that they could refrain from participating in the study at any time without consequences for future care, and all the patients who agreed to participate gave their verbal consent.

### *Examination and treatment schedule*

The patients were included in the study if the condition was in concordance with the above criteria. Microdialysis was performed at two separate visits 2 weeks apart. Local administration of glucocorticoid was performed at the first visit.

### *Assessment of subjective symptoms*

A 100-mm visual analogue scale (VAS) (ACO, Stockholm, Sweden) with end points marked with 'No pain' and 'Worst pain ever experienced' was used to assess the average pain intensity in the masseter region at rest during the past week. The duration of local pain in the masseter region and of general muscle pain was recorded.

### *Clinical examination*

The most tender point (PMT) of the masseter muscle on

any side was determined by digital palpation and recorded on a schematic figure. This point was used for all further investigations of the masseter muscle. The degree of masseter muscle tenderness on the most tender side (TDP) was assessed with a three-graded scale, where 0 = no tenderness, 1 = mild to moderate tenderness, and 2 = moderate to strong tenderness with a palpebral reflex. Maximum voluntary mouth opening (MVM) was measured in millimeters between incisors 11 and 41. Pain on MVM (PMVM) was recorded as present or absent on the TDP. The pressure pain threshold (PPT) to linearly increasing pressure over the PMT was assessed with an algometer (Pain Diagnostics and Thermography Co., Great Neck, N.Y., USA) using a pressure rate of 50 kPa/sec. The tip of the algometer had an area of 1.0 $cm^2$, and the pressure was applied perpendicularly to the skin surface.

### *Microdialysis*

Microdialysis was performed immediately after the clinical examination at both visits. A standard disposable catheter (Venflon 2, BOC Ohmeda AB, Helsingborg, Sweden; diameter, 1.2 mm) was inserted into the PMT after skin surface anesthesia with EMLA® cream (lidocaine, 25 mg; prilocaine, 25 mg/g; Astra AB, Södertälje, Sweden) for 20 min. EMLA cream provides complete skin surface anesthesia that does not progress into underlying muscle tissue (19). The probe used for the dialysis (CMA 10, Carnegie Medicine, Stockholm, Sweden) has an outer diameter of 0.65 mm and was inserted via the standard catheter to a depth of 19 mm from the skin surface. The membrane of the probe has a length of 10 mm, a diameter of 0.50 mm, and a molecular cut-off of 20 KU. Microdialysis was performed with physiological saline (9 mg NaCl/mL; Kabi Pharmacia, Uppsala, Sweden) as perfusion medium at a flow-rate of 7 μL/min during 30 min for each sample. Three consecutive samples were obtained from each individual. The mean level of M-$PGE_2$ and M-$LTB_4$ in these samples was calculated as an estimation of the intramuscular level and used for statistical analysis in this study. The relative in vitro recovery of the probes with regard to $PGE_2$ and $LTB_4$ was investigated before the clinical samplings. The mean (standard deviation (*s*)) recovery was 22% (4%) for $PGE_2$ and 30% (21%) for $LTB_4$.

### *Glucocorticoid administration*

Intramuscular injection of 0.3 mL methylprednisolone (Depo-Medrol®, 40 mg/mL; Upjohn, Kalamazoo, Mich., USA) was performed bilaterally into the PMT after the microdialysis at visit 1.

### *Blood examination*

A total of 25 mL venous blood was collected from each patient immediately before the clinical examination and distributed into three tubes. One tube containing sodium citrate was used to determine the erythrocyte sedimentation rate (ESR), and another tube was used for analysis of the serum concentration of C-reactive protein (CRP). ESR was considered abnormal when >20 mm/h and CRP when >10 mg/L. Still another tube containing ethylenediaminetetraacetic acid (EDTA) was immediately centrifuged for 10 min at 1500 *g* and 4°C. Ninety microliters of the supernatant was pipetted into an Ependorph tube containing 4.5 μL indomethacin and 4.5 μL 4M HAC (Author: Please explain HAC) for analysis of plasma levels of $PGE_2$ (P-$PGE_2$), and 120 μL was pipetted into another Ependorph tube for analysis of plasma levels of $LTB_4$ (P-$LTB_4$). The samples were then immediately frozen (−80°C).

### *Analyses*

The sample concentrations of $PGE_2$ were analyzed in duplicate with a commercially available radioimmunoassay kit (NEN Du Pont Research Products, Boston, Mass., USA). This $PGE_2$ assay has 30% cross-reactivity with $PGE_1$ but less than 0.9% with other substances. The detection limit was 0.5 pg/mL, and the sensitivity 4.4 pg/mL.

The concentration of $LTB_4$ in the samples was determined with a commercially available radioimmunoassay kit (NEK-037, Du Pont de Nemours & Co. Medical Products, Boston, Mass., USA) with a detection limit of 12 pg/mL and a sensitivity of 50 pg/mL.

### *Statistics*

The Kolmogorov–Smirnov test was used to test for normality. $PGE_2$ and $LTB_4$ were found not to be normally distributed, and therefore non-parametric statistical methods were used. The significance of the changes in $PGE_2$ and $LTB_4$ concentrations after treatment were tested with the Wilcoxon test, and the differences between groups with regard to changes in $PGE_2$ and $LTB_4$ after treatment were tested with the Mann–Whitney U-test. The significance of the correlations between $PGE_2$ and $LTB_4$ levels and other variables was tested with the Spearman ranked correlation test. The level of significance was set to $P < 0.05$.

## Results

Variables related to the individual in the two patient groups are shown in Table 1, whereas masseter muscle-related variables are shown in Table 2. None of the patients had an abnormal ESR, but on an average it was higher among the fibromyalgia patients than in the local myalgia patients ($P = 0.006$). Two patients in the fibromyalgia group had increased CRP levels (27 and 142 mg/L, respectively). There were no significant differences before treatment between the two groups with regard to age, sex, M-$PGE_2$, M-$LTB_4$, P-$PGE_2$, or P-$LTB_4$.

Table 2. Masseter muscle pain and intramuscular levels of $PGE_2$ and $LTB_4$ in 18 patients with fibromyalgia and 15 with localized myalgia of the masseter muscle, before and after local glucocorticoid administration

| | Before treatment | | | After treatment | | | |
|---|---|---|---|---|---|---|---|
| | M | IQR | *n* | M | IQR | *n* | *P* |
| Fibromyalgia | | | | | | | |
| VAS | 55 | 55 | 18 | 50 | 40 | 18 | |
| PPT | 61 | 25 | 18 | 98 | 43 | 18 | * |
| TDP | 2 | 0 | 18 | 1 | 1 | 18 | * |
| PMVM | 1 | 1 | 18 | 0 | 1 | 18 | * |
| M-$PGE_2$ | 5 | 26 | 18 | 11 | 18 | 18 | * |
| M-$LTB_4$ | 44 | 99 | 15 | 120 | 158 | 16 | * |
| Local myalgia | | | | | | | |
| VAS | 60 | 30 | 15 | 40 | 63 | 14 | |
| PPT | 74 | 25 | 15 | 98 | 49 | 15 | * |
| TDP | 2 | 0 | 15 | 1 | 1 | 15 | * |
| PMVM | 1 | 1 | 15 | 1 | 1 | 15 | |
| M-$PGE_2$ | 7 | 43 | 15 | 8 | 20 | 15 | |
| M-$LTB_4$ | 6 | 64 | 15 | 56 | 87 | 15 | * |

M = median, IQR = interquartile range, and *n* = number of observations. VAS = visual analogue scale score (0–100) for masseter muscle resting pain, PPT = pressure pain threshold (kPa) over the masseter muscle, PMVM = pain in the masseter muscle region on maximum voluntary mouth opening, TDP = tenderness to digital palpation of the masseter muscle (0–2), M-$PGE_2$ = masseter muscle dialysate level of prostaglandin $E_2$ (pg/mL), M-$LTB_4$ = dialysate level of leukotriene $B_4$ (pg/mL). *P* values for the difference before and after treatment are denoted by * for $P < 0.05$.

### *Effect on intramuscular prostaglandin $E_2$ and leukotriene $B_4$*

M-$PGE_2$ did not change significantly after glucocorticoid administration in any of the groups (Fig. 1).

M-$LTB_4$ increased in both patient groups (FM, $P = 0.005$, and LM, $P = 0.038$, respectively) (Fig. 1). Changes in M-$PGE_2$ and M-$LTB_4$ were positively correlated to each other in the two groups combined ($r_s = 0.37$, $n = 30$, $P = 0.046$).

### *Effect on plasma levels of prostaglandin $E_2$ and leukotriene $B_4$*

In the patients with local myalgia P-$LTB_4$ increased after glucocorticoid administration ($P = 0.042$) (Fig. 1). No other significant changes with regard to P-$PGE_2$ or P-$LTB_4$ were found.

### *Correlation between changes in $PGE_2$ and $LTB_4$ and effects on clinical variables*

*Fibromyalgia group*. The changes in M-$PGE_2$ that occurred on treatment were positively correlated to the changes in the VAS ($r_s = 0.52$, $n = 18$, $P = 0.026$) (Fig. 2); that is, decrease in M-$PGE_2$ was associated with decrease in the VAS. The changes in MVM were negatively correlated to the changes in M-$PGE_2$ ($r_s = -0.59$, $n = 18$, $P = 0.009$) (Fig. 2); that is, increase in MVM was associated with decrease in M-$PGE_2$. The changes in the VAS were negatively correlated to the changes in P-$LTB_4$ ($r_s = -0.59$, $n = 14$, $P = 0.026$) (Fig. 3); that is, the decrease in the VAS was associated with an increase in P-$LTB_4$.

*Local myalgia group*. The changes in M-$LTB_4$ were positively correlated to the changes in P-$LTB_4$ ($r_s = 0.60$, $n = 11$, $P = 0.048$), with increase in P-$LTB_4$ associated with increase in M-$LTB_4$. The changes in TDP of the masseter muscle were negatively correlated with the changes in P-$LTB_4$ ($r_s = -0.67$, $n = 11$, $P = 0.024$), and decrease in TDP was thus associated with increase in P-$LTB_4$.

### *Background factors*

*Fibromyalgia group*. The changes in VAS after glucocorticoid administration were negatively correlated to the M-$PGE_2$ level before treatment ($r_s = -0.64$, $n = 18$, $P = 0.004$), which means that the higher the level of M-$PGE_2$ before treatment, the more reduction in the VAS.

*Local myalgia group*. The changes in M-$PGE_2$ were negatively correlated to age ($r_s = -0.55$, $n = 15$, $P = 0.032$), and decrease in M-$PGE_2$ was therefore more pronounced in the older patients. The changes in P-$LTB_4$ were also negatively correlated with age ($r_s = -0.63$, $n = 11$, $P = 0.038$) but positively with the changes in M-$LTB_4$ ($r_s = 0.60$, $n = 11$, $P = 0.048$), which means that decrease in P-$LTB_4$ is more pronounced in older patients and is associated with decrease in M-$LTB_4$.

### *Group differences with regard to treatment effect on mediators*

There were no significant differences between the groups with regard to treatment effects on muscle or plasma levels of $PGE_2$ and $LTB_4$ after intramuscular administration of glucocorticoid, but there was a tendency for P-$LTB_4$ to increase more in the local myalgia patients than in the fibromyalgia patients ($P = 0.075$).

## Discussion

This study shows that the interindividual variation in the

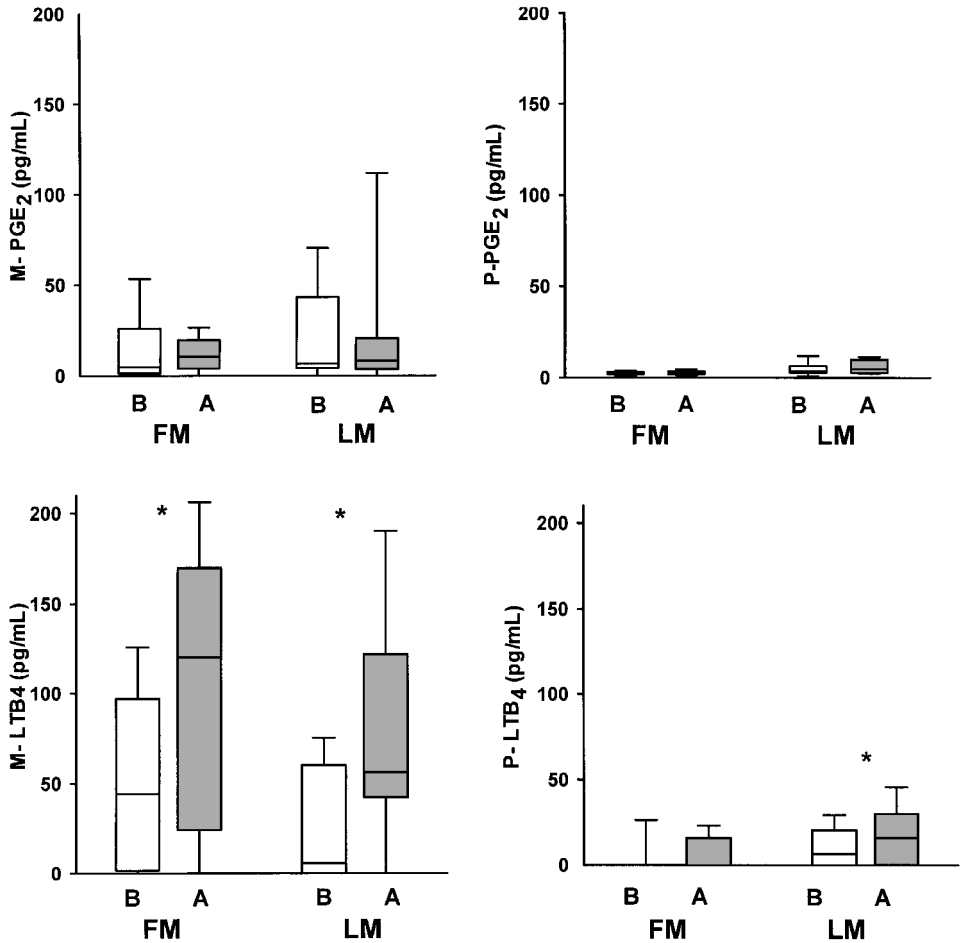


Fig. 1. Panel showing box-plots (10th, 25th, 50th, 75th, and 90th percentiles) of the distribution of masseter muscle dialysate levels and plasma levels of prostaglandin $E_2$ (M-$PGE_2$, P-$PGE_2$), and leukotriene $B_4$ (M-$LTB_4$, P-$LTB_4$) for 18 patients with fibromyalgia (FM) and 15 patients with local myalgia (LM) in the temporomandibular system before (B) and 2 weeks after (A) local intramuscular administration of glucocorticoid. In both the FM and LM groups the dialysate levels of M-$LTB_4$ increased after treatment ($P = 0.005$ and $P = 0.038$, respectively), as did the level of P-$LTB_4$ in the patients with LM ($P = 0.042$). * $P < 0.05$.

response of M-$PGE_2$ to glucocorticoid 2 weeks after local administration is large in both groups, and there is no consistent change. However, the reductions in the levels of this mediator that did occur were associated with corresponding reductions of pain in the fibromyalgia group. On the other hand, M-$LTB_4$ was found to increase in both groups after glucocorticoid administration. The reason for this increase is unknown at present. Methods, subjects, and tissue type in previous studies differ from our study, making it difficult to make comparisons. Invasive techniques such as microdialysis seem to cause local prostaglandin synthesis (20). $PGE_2$ has been found in TMJ synovial fluid in an animal study, where it was collected by microdialysis from the superior joint space (21). Detectable and steady levels of $PGE_2$ in that study were obtained during the whole experimental period of 240 min. The placement of a catheter in the superior joint space of the TMJ thus provided sufficient trauma to cause a minimal but detectable level of $PGE_2$ in the synovial fluid. There is reason to expect a similar reaction in muscle tissue. With regard to our study, it is assumed that the impact of the needle puncture and the ensuing microdialysis procedure would be similar at the two examinations and that a difference in response should be due to the treatment given.

The intramuscular injection of methylprednisolone did not cause a reduction of M-$PGE_2$, as measured 2 weeks after injection, in any of the two groups. This finding is in agreement with the animal experimental study by Swift et al. (21), in which dexamethasone administered into the rabbit TMJ did not influence the local production of $PGE_2$, and with a study of the human knee joint with inflammatory arthritides (22).

The lack of significant change in dialysate level of M-

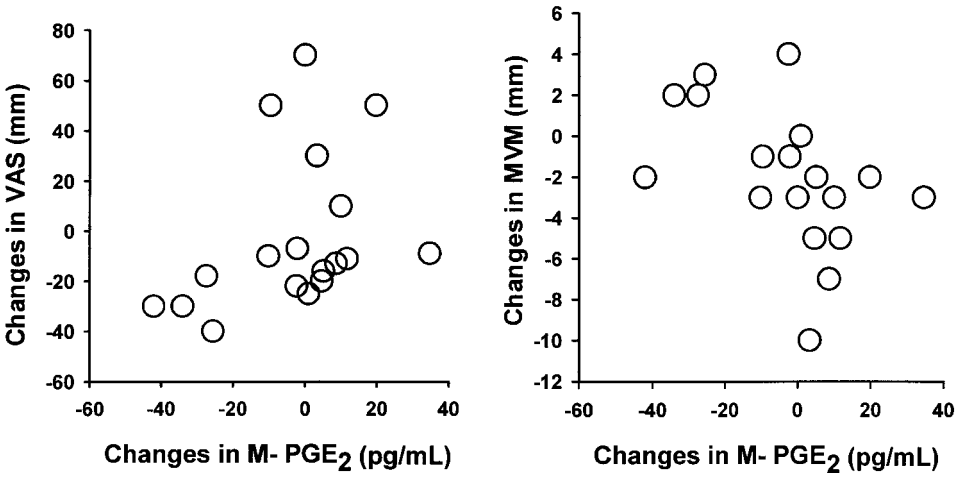


Fig. 2. Scatterplot panel showing relations between changes in masseter muscle dialysate levels of prostaglandin $E_2$ (M-$PGE_2$) and clinical variables 2 weeks after local intramuscular administration of glucocorticoid in 18 patients with fibromyalgia. There were correlations between changes in M-$PGE_2$ and changes in resting pain (VAS) ($r_s = 0.52$, $n = 18$, $P = 0.026$) and between changes in M-$PGE_2$ and changes in maximum voluntary mouth opening (MVM) ($r_s = -0.59$, $n = 18$, $P = 0.009$). Positive values on the axes denote increase, and negative values denote decrease of the variables after treatment.

$PGE_2$ after local intramuscular administration of glucocorticoid in spite of reduction of pain and tenderness indicates that other mediators could be involved in the modulation of resting pain in the masseter muscle in both groups. For instance, bradykinin has been shown to decrease after intra-articular administration of glucocorticoid in an animal study with experimental inflammation (21). The interindividual variation in the level of M-$PGE_2$ before treatment may also be a factor of importance, since the reduction in resting pain was correlated to the pretreatment level of M-$PGE_2$. The 2-week interval between the two microdialysis examinations and the size of the dose of glucocorticoid may also be a factor contributing to the lack of consistent change of $PGE_2$. The muscle is densely vascularized, and it can be assumed that a considerable part of the drug is eliminated from the muscle tissue rather quickly. The tissue levels of glucocorticoid are in fact unknown at any time after injection into the muscle. However, a decrease in resting pain and an increase of MVM seem to occur in parallel with decrease of M-$PGE_2$ in fibromyalgia patients. The finding that a decrease in M-$PGE_2$ is associated with reduction of pain after treatment and that patients with high levels of $PGE_2$ before treatment showed a larger decrease of resting pain than the patients with a low level indicates that $PGE_2$ takes part in the modulation of masseter muscle pain in fibromyalgia. There are probably individual differences in the contribution of $PGE_2$ to pain among fibromyalgia patients due to contributions of other pain mediators. The intramuscular level of serotonin has been shown to decrease after local glucocorticoid treatment and to be associated with a corresponding reduction of pain (23). This might be the effect of a reduced number of mast cells in the tissue after local glucocorticoid administration. Serotonin is released from mast cells or thrombocytes after and during tissue trauma (24), and an increased number of mast cells has been reported in the muscle tissue of patients with fibromyalgia (25).

M-$LTB_4$ was increased in the masseter muscle 2 weeks after local glucocorticoid administration in both patient groups. The reason for this increase is unknown. The increase in M-$LTB_4$ was not related to an increase in plasma level in the fibromyalgia patients but was so in the local myalgia patients. The associations between increase

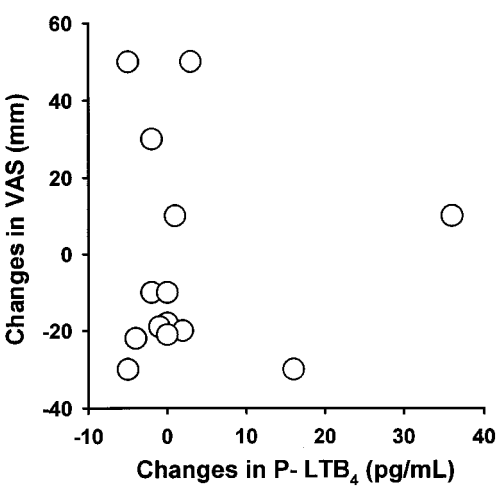


Fig. 3. Scatterplot showing the relations between changes in plasma levels of leukotriene $B_4$ (P-$LTB_4$) and intensity of masseter muscle resting pain (VAS) 2 weeks after administration of glucocorticoid into the masseter muscle in 15 patients with fibromyalgia (FM). There was a negative correlation between changes in P-$LTB_4$ and changes in VAS ($r_s = -0.69$, $n = 14$, $P = 0.026$).

of P-$LTB_4$ and decrease of pain in the patients with fibromyalgia and between increase of P-$LTB_4$ and decrease of hyperalgesia in the patients with local myalgia cannot be explained yet. On the contrary, $LTB_4$ has been shown to induce hyperalgesia in behavioral experiments (11) and to act as an inflammatory mediator in several immune-mediated diseases, such as rheumatoid arthritis, psoriasis, and chronic inflammatory bowel disease (26).

$LTB_4$ has been detected in microdialysis samples from non-painful masseter muscle (12) and in plasma samples from healthy individuals. The former finding probably means that the trauma caused by puncture and the microdialysis probe insertion is severe enough to elicit local intramuscular production and release of $LTB_4$. Detectable plasma levels of $LTB_4$ have been found in healthy individuals in several studies (27, 28).

The results of this study are compatible with the hypothesis that $PGE_2$ and $LTB_4$ play a role in muscle pain modulation and that inflammatory components are present in fibromyalgia, although it is not a primary inflammatory disorder. This condition has also been suggested to be partly of peripheral inflammatory origin and partly due to central mechanisms (29).

It can be concluded that even though the masseter muscle level of $PGE_2$ is not consistently influenced by intramuscular glucocorticoid administration, reduction of this level is associated with decrease of masseter muscle resting pain in patients with fibromyalgia. On the other hand, the masseter muscle level of $LTB_4$ seems to increase in patients with fibromyalgia and localized myalgia after local glucocorticoid administration.

*Acknowledgements.*—The authors would like to express their appreciation to Ebba Lagerkrans and Lena Johansson for skillful clinical assistance and laboratory work. This study was financially supported by grants from the Institute of Odontology, Karolinska Institutet, and the Swedish Dental Association.

## References

1. Layzer R. Muscle pain, cramps, and fatigue. In: Engel AG, Franzini, Armstrong C, editors. Myology. 2nd ed. New York: Health Profession Division, McGraw-Hill Inc.; 1994. p. 1754–68.
2. Calliet R. Myofacial pain syndromes. In: Calliet R, editor. Head and face pain syndromes. Philadelphia: F. A. Davis; 1992. p. 100–24.
3. Wilson JR, Kapoor SC. Contribution of prostaglandins to exercise-induced vasodilation in humans. Am J Physiol 1993;265 (1 Pt 2):H171–5.
4. Flower RJ, Blackwell GJ. The importance of phospholipase $A_2$ in prostaglandin biosyntesis. Biochem Pharm 1976;225:285–91.
5. Wittenberg RH, Willburger RE, Kleemeyer KS, Peskar BA. In vitro release of prostaglandins and leukotrienes from synovial tissue, cartilage, and bone in degenerative joint diseases. Arthritis Rheum 1993;36:1444–50.
6. McLennan IS, Macdonald RE. Prostaglandin syntetase and prostacyclin synthetase in mature rat skeletal muscles: immunohistochemical localization to arterioles, tendons and connective tissues. J Anat 1991;178:243–53.
7. Lam BK, Austen KF. Leukotrienes: biosyntesis, release and actions. In: Gallin JI, Goldstein IM, Snytderman R, editors. Inflammation: basic principles and clinical correlates. New York: Raven Press Ltd; 1992. p. 139–47.
8. Samuelsson B. Arachidonic metabolism: role in inflammation. Rheumatology 1991;50 Suppl 1;3–6.
9. Levine JD, Taiwo YO. Hyperalgesic pain: a review. Anesth Prog 1990;37:133–5.
10. Ahmadazadeh N, Shingu M, Nobunaga M, Tawara T. Relationship between leukotriene B4 and immunological parameters in rheumatoid synovial fluids. Inflammation 1991;5:497–503.
11. Samuelsson B, Dahlen S-E, Lindgren JÅ, Rouzer CA, Serhan CN. Leukotrienes and lipoxins: structures, biosynthesis and biological effects. Science 1987;237:1171–6.
12. Hedenberg-Magnusson B, Ernberg M, Alstergren P, Kopp S. Pain mediation by prostaglandin $E_2$ and leukotriene $B_4$ in the human masseter muscle. Acta Odontol Scand 2001;59:348–55.
13. Lacronique J, Russo-Marie F, Marsac J. Mechanism of action and effects of corticoids in asthma. Rev Mal Respir 1989;6:15–30.
14. Hirata F, Sciffman E, Venkastasubramanian K, Salomon D, Axelrod J. A phospholipase A2 inhibitory protein in rabbit neutrophils induced by glucocorticoids. Proc Natl Acad Sci USA 1980;77:2533–6.
15. Clark S, Tindall E, Bennet RM. A double blind crossover trial of prednisolone versus placebo in the treatment of fibrositis. J Rheumatol 1985;12:980–3.
16. Ernberg M, Hedenberg-Magnusson B, Alstergren P, Kopp S. Short-term effect of glucocorticoid injection into the superficial masseter muscle of patients with chronic myalgia: a comparison between fibromyalgia and localized myalgia. J Orofac Pain 1997;11:249–57.
17. Wolfe F, Smythe H, Yunus MB. The American College of Rheumatology: criteria for the classification of fibromyalgia. Arthritis Rheum 1990;33:160–72.
18. Okeson JP. Differential diagnosis and management considerations of temporomandibular disorders. Orofacial pain: guideline for assessment, diagnosis and management. Chicago: Quintessence Publishing Co., Inc; 1996. p. 113–4.
19. Bjerring P, Arent-Nielsen L. Depth and duration of skin analgesia to needle insertion after topical application of EMLA cream. Br J Anaesth 1990;64:173–7.
20. Willians TJ. Interactions between prostaglandins, leukotrienes and other mediators of inflammation. Br Med Bull 1983;3:239–42.
21. Swift JQ, Roszkowski MT, Alton T, Hargreaves KM. Effect of intra-articular versus systemic anti-inflammatory drugs in a rabbit model of temporomandibular joint inflammation. J Oral Maxillofac Surg 1988;56:1288–95.
22. Bombardieri S, Cattani P, Di Munno I, Pasero G, Patrono C, Pinca E, et al. The synovial prostaglandin system in Chronic inflammatory arthritis: differential effects of stereoidal and nonstereoidal anti-inflammatory drugs. J Pharmacol 1981;73: 893–901.
23. Ernberg M, Hedenberg-Magnusson B, Alstergren P, Kopp S. Effect of local glucocorticoid injection on masseter muscle level of serotonin in patients with chronic myalgia. Acta Odontol Scand 1998;3:129–34.
24. Hindle AT. Recent developments in the physiology and pharmacology of 5-hydroxytrypramine. Br J Anaesth 1994;73: 395–407.
25. Eneström S, Bengtsson A, Lindström F, Johan K. Attachment of IgG to dermal extracellular matrix in patients with fibromyalgia. Clin Exp Rheumatol 1990;8:127–35.
26. Thomsen MK, Ahnfelt-Ronne I. Leukotrienes. A review of the significance for disease in man and the possibilities for the therapeutic intervention. Ugeskr Laeger 1991;14:173–6.
27. Lam BK, Austen KF. Leukotrienes: biosynthesis, release and actions. In: Gallin JI, Goldstein IM, Snyderman R, editors.

Inflammation: basic principles and clinical correlates. New York: Raven Press Ltd; 1992. p.139–47.
28. Mantegazza R, Bernasconi P. Cellular aspects of myositis. Curr Opin Rheumatol 1994;6:568–74.
29. Elert JE, Rantapaa-Dahlquist SB, Henriksson-Larsen K, Lorentzon R, Gerdle BU. Muscle performance, electromyography and fibre type composition in fibromyalgia and work-related myalgia. Scand Rheumatol 1992;21:28–34.

Received for publication 26 March 2001
Accepted 24 July 2001