Randomized Trial

Does Acetaminophen Activate Endogenous Pain Inhibition in Chronic Fatigue Syndrome/ Fibromyalgia and Rheumatoid Arthritis? A Double-Blind Randomized Controlled Cross-over Trial

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Background: Although enhanced temporal summation (TS) and conditioned pain modulation (CPM), as characteristic for central sensitization, has been proved to be impaired in different chronic pain populations, the exact nature is still unknown.

Objectives: We examined differences in TS and CPM in 2 chronic pain populations, patients with both chronic fatigue syndrome (CFS) and comorbid fibromyalgia (FM) and patients with rheumatoid arthritis (RA), and in sedentary, healthy controls, and evaluated whether activation of serotonergic descending pathways by acetaminophen improves central pain processing.

Study Design: Double-blind randomized controlled trial with cross-over design.

Methods: Fifty-three women (19 CFS/FM patients, 16 RA patients, and 18 healthy women) were randomly allocated to the experimental group (1 g acetaminophen) or the placebo group (1 g dextrose). Participants underwent an assessment of endogenous pain inhibition, consisting of an evaluation of temporal summation with and without conditioned pain modulation (CPM). Seven days later groups were crossed-over. Patients and assessors were blinded for the allocation.

Results: After intake of acetaminophen, pain thresholds increased slightly in CFS/FM patients, and decreased in the RA and the control group. Temporal summation was reduced in the 3 groups and CPM at the shoulder was better overall, however only statistically significant for the RA group. Healthy controls showed improved CPM for both finger and shoulder after acetaminophen, although not significant.

Limitations: The influence of acetaminophen on pain processing is inconsistent, especially in the patient groups examined.

Conclusion: This is the first study comparing the influence of acetaminophen on central pain processing in healthy controls and patients with CFS/FM and RA. It seems that CFS/FM patients present more central pain processing abnormalities than RA patients, and that acetaminophen may have a limited positive effect on central pain inhibition, but other contributors have to be identified and evaluated.

Key words: Chronic pain, sensitization, acetaminophen, conditioned pain modulation, temporal summation, chronic fatigue syndrome, fibromyalgia, rheumatoid arthritis

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Chronic pain is the most debilitating symptom in many medical conditions including fibromyalgia (FM), chronic fatigue syndrome (CFS), chronic low back pain, rheumatoid arthritis (RA), osteoarthritis, and chronic whiplash. An increasing amount of scientific evidence indicates that central sensitization (CS) accounts for chronic pain in the majority of these patients (1- 6).

Sensitivity to pain results from the outcome of the battle between pain facilitatory and inhibitory pathways. One function of the descending inhibitory pathway is to "focus" the excitation of the dorsal horn neurons by suppressing surrounding neuronal activity (7), a role attributed to the conditioned pain modulation (CPM) phenomenon (8). In chronic pain and CS, the descending pain-inhibitory pathways, including CPM, seem to be malfunctioning, e.g., in patients with CFS, FM, osteoarthritis, etc. (1,2,4). Malfunctioning of CPM is however not proven in all chronic pain populations. For example, one study reported normal function in RA patients (9). However, the symmetrical manifestation of RA, the poor relation between the arthritis's activity and symptoms, and the generalized hyperalgesia both at articular and non-articular sites for different kinds of stimuli are indicative for CS in RA patients (10).

Another characteristic of CS is enhanced wind-up of the dorsal horn neurons or temporal summation (TS) of second pain (5). Wind-up refers to the progressive increase of electrical discharges from the second-order neurons in the spinal cord in response to repetitive C-fiber stimulation, and is experienced in humans as increased pain (11-13). In healthy controls CPM is able to soften TS (14), which may protect the central nervous system (CNS) from excessive nociceptive barrage. In patients with FM and RA there is already evidence for enhanced TS of pain (5,15-17), but the possible contribution of impaired pain inhibition is still unclear.

Descending control of pain entails an extremely sophisticated grouping of CNS actions [reviewed in (18)]. Acetaminophen primarily acts centrally: it reinforces descending inhibitory pathways (19), namely the serotonergic descending pain pathways (20). In addition, acetaminophen may exert an inhibitory action on the enzyme cyclooxygenase in the CNS, involved in the transformation of arachnidonic acid to prostaglandins. Cyclooxygenase-2 and prostaglandin E2 expression in the CNS takes part of the mechanism of CS in those with chronic pain (21). The fact that several genotypes of the serotonin gen are related to higher levels of pain intensity in patients with CS (22,23) further supports the hypothesis that activating serotonergic descending pathways improves CPM and the suppressing of TS in patients' CS.

This rationale remains speculative and has not yet been evaluated in chronic pain patients.

Objectives

Therefore, the manifestation of TS, the efficacy of CPM, and the influence of acetaminophen on these mechanisms will be evaluated. This will be done in healthy controls; in patients with CFS and FM, syndromes that are predominantly characterised by CS; and in another chronic pain population, patients with RA, in which CS could also play a role besides the peripheral (articular) problems (10). Here, we report the outcome of a double-blind randomized cross-over controlled trial examining these mechanisms in 53 patients.

METHODS

A single-dose, randomized, double-blind, 2-period cross-over design was used. The study took place at the Research Unit of the University Hospital Antwerp (Belgium) and was approved by the ethical committee of the University Hospital Antwerp and the Federal Agency for Medicines and Health Products (EUDRA CT number 2010-020498-17) and is registered by ClinicalTrials.gov (NCT01154647).
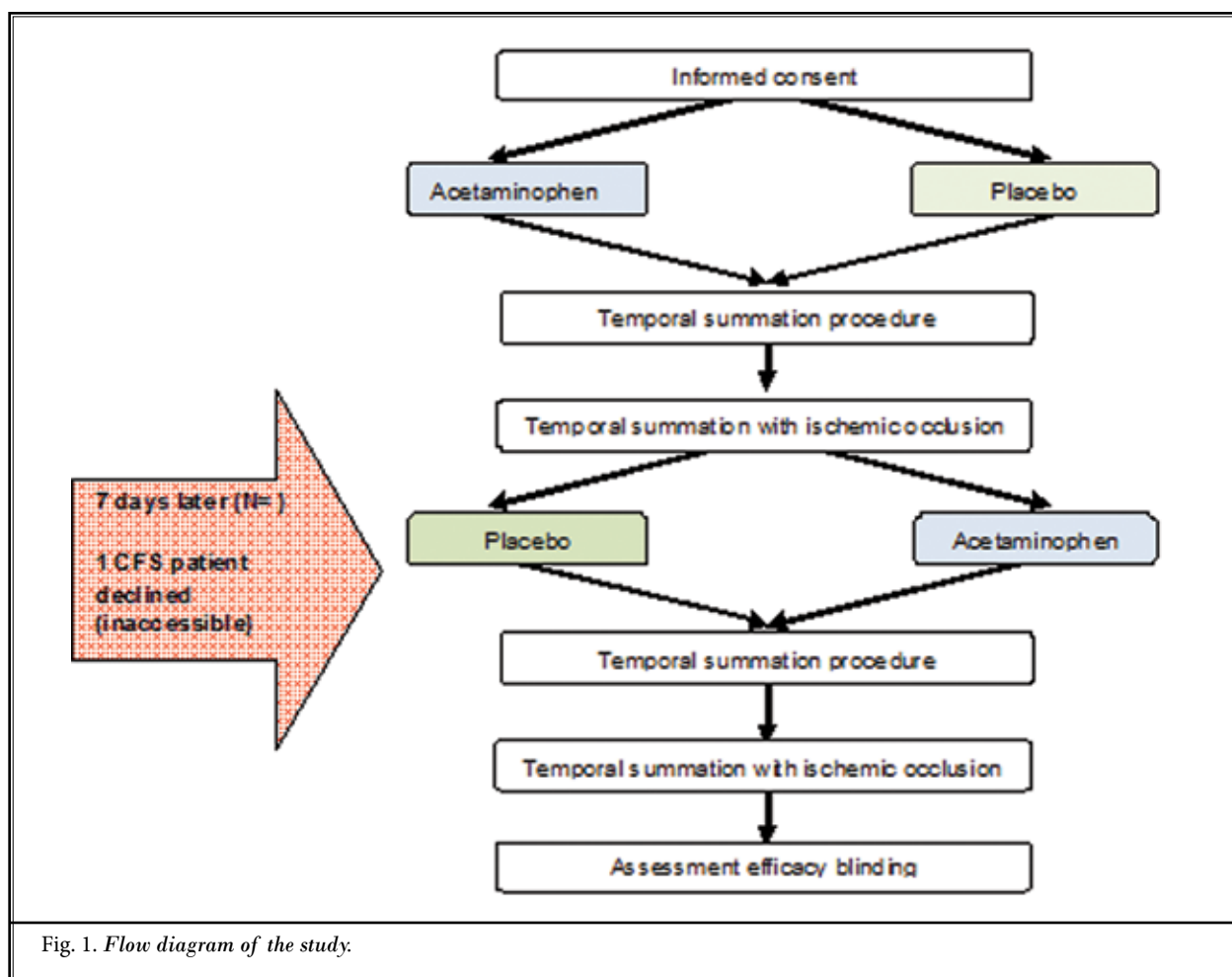
Patients

The present study aimed at enrolling 2 chronic pain populations: those with RA and those with a typical central sensitization image, patients fulfilling the criteria for both CFS and primary FM. Furthermore, healthy sedentary pain-free subjects were included as controls. Each study participant was a woman aged between 23 and 69 years. The CFS/FM group complied with the diagnostic criteria for FM as defined by the American College of Rheumatology (24) and the Center of Disease Control criteria for CFS (25), this means that their pain and fatigue complaints could not be the result of a medical diagnoses of cancer, RA, multiple sclerosis, psychiatric illnesses, etc. At the time of inclusion, healthy control subjects could not have any pain complaints. Sedentary was defined as having a sedentary job and performing less than 3 hours of moderate physical activity per week. Moderate physical activity was defined as activity demanding at least the threefold of the energy spent passively (26). In order to preclude confounding factors, participants could not be pregnant or until one year postnatal and were asked to stop antidepressants and

other medication 2 weeks prior to study participation, not to undertake physical exertion, and to refrain from consuming caffeine, alcohol, or nicotine on the day of the experiment. For ethical reasons, patients were able to take non-opioid pain medication as described in the first step of the World Health Organization analgesic ladder (NSAID's and acetaminophen) up to 48 hours before the experiment.

Based on an a priori power analysis we aimed at enrolling a total sample size of at least 39 patients. Sample size was calculated based on a power analysis, calculated with G*Power 3.1.3. An a priori power analysis was performed for the within-between interaction in repeated measures ANOVA with 3 groups, 4 measurements (TS with and without CPM, under placebo or acetaminophen), an effect size of .25 and a minimum power of .90.

Procedure

Before patients were subjected to the experiment, they received all the information needed and were asked to sign the informed consent. This experiment was a double-blind randomized controlled trial (RCT) with cross-over design, as presented in Fig. 1. In order to evaluate whether activation of serotonergic descending pathways improved pain inhibition, patients were allocated to a placebo group or an experimental group that received acetaminophen per os. The experiment consisted of an evaluation of the manifestation of TS with and without a conditioning stimulus. This protocol was repeated in the cross-over design (experimental groups became control group and vice versa) with a one-week washout period.

Fig. 1. *Flow diagram of the study.*

Acetaminophen and Placebo

Both placebo (1g dextrose) and acetaminophen (1g acetaminophen) were capsuled in 2 hard gelatin capsules, allowing blinding of patients and researchers. Capsules were administered per os 30 minutes before the assessment of pain inhibition, given the pharmacokinetic profile of acetaminophen. Following oral administration, acetaminophen is rapidly and almost completely absorbed from the gastro-intestinal tract. Peak plasma concentrations are attained within 10 – 60 minutes. It is distributed into most body tissues. Plasma protein binding is negligible at usual therapeutic doses but increases with increasing doses. The elimination half-life varies from about one to 3 hours. Acetaminophen is a p-aminophenol derivative that exhibits analgesic and antipyretic activity.

Capsules were delivered by a study nurse who coordinated the randomized allocation (by a computer program). This way, both the patients and the rater remained blinded until the end of the study. At the end of the study the efficacy of the blinding was evaluated in both patients and rater.

Endogenous Pain Inhibition

The efficacy of endogenous pain inhibition was assessed by a procedure of temporal and spatial summation of noxious stimuli, as described by Cathcart et al (14). This procedure evaluates the degree of TS or wind-up in response to 10 applications (pulses) of the Fisher algometer (Force Dial model FDK 40, Wagner Instruments, Greenwich) at a previously defined pressure pain threshold intensity at the dorsal surface of the right-hand middle finger midway between the first and second distal joints, and at the middle of the right-hand side upper trapezius belly. The subjects were asked to rate the intensity and unpleasantness of the pain intuitively of the first, fifth, and tenth pulse on a verbal numerical rating scale (VNRS) (0 = no pain to 10 = worst possible pain). CPM was assessed by replicating the TS assessment associated with a conditioning stimulus for eliciting CPM. The conditioning stimulus was an occlusion cuff at the left arm inflated to a painful intensity and maintained at the level while TS was elicited. This procedure is explained in depth elsewhere and seemed reliable. In healthy controls CPM induced by the ischaemic cuff is able to dampen TS (14). The same method was previously used in chronic whiplash patients (27).

The outcome measure for TS is the difference between the tenth and the first pain rating score before cuff inflation. The measure for CPM is the difference between the tenth pain rating score before occlusion and the tenth during occlusion. This means that 8 TS scores (TS1–TS4: under placebo and TS5–TS8: under acetaminophen) and 4 CPM (CPM1–2: under placebo and CPM3–4: under acetaminophen) scores were obtained per test site (finger and shoulder) for each participant.

Statistical Analysis

All data were analyzed using the Statistical Package for Social Sciences 20.0 for Windows (SPSS Inc. Headquarters, Chicago, Illinois, USA). Normality of data was assessed with the one sample Kolmogorov-Smirnov test. Descriptives are presented as means ± standard deviations. Baseline characteristics were compared between groups with a one-way ANOVA. As age was significantly higher in patients with RA, further analyses were corrected for age. Changes in TS and in CPM were compared between the 3 groups by repeated measures ANCOVAS. Changes in PPT's between placebo and acetaminophen within groups were evaluated with paired t-tests and effect sizes were calculated as Cohen's d, with d defined as the difference between the 2 means divided by the pooled standard deviation for those means. A d-value of .20 is described as small, .50 as medium (moderate), and .80 as large (28).

Significance level was set at 0.05.

Results

Fifty-three volunteers participated in the study (19 CFS/FM patients, 16 RA patients, and 18 healthy controls), all women between 23 and 69 years old. One CFS/FM patient withdrew from the study because she forgot the second appointment and did not show up at a second attempt. Because the mean age (Table 1) was significantly higher in the RA group, analysis of the pain scores are age corrected, although this did not change the results.

Comparison of Characteristics under Placebo

Pain thresholds at the finger were significantly higher in the control group compared to the 2 patient groups and pain thresholds at the shoulder were significantly lower in the CFS/FM group compared to the RA patients and the controls.

Also the threshold for the cuff pressure was significantly lower in the CFS/FM group, accompanied by higher VNRS scores for the experienced ischemic pain. At a VNRS-score of 3 (as defined by Cathcart et al [14]), the cuff pressure was again statistically

Table 1. *Age and pain score under acetaminophen and placebo.*

	CFS/FM (n=19)*		RA (n=16)		CON (n=18)		Significant differences
	Mean	SD	Mean	SD	Mean	SD	
Age	44.58	7.34	54.25	8.36	41.06	14.48	RA > CON = CFS
PPT finger	6.00	2.26	6.63	2.71	8.50	1.86	CON > CFS = RA
PPT finger	5.80	2.49	6.73	3.09	9.53	2.50	CON > CFS = RA
PPT shoulder	2.05	1.27	4.13	2.36	4.89	1.94	CFS < CON = RA
PPT shoulder	1.83	0.82	4.19	3.04	5.19	2.07	CFS < CON = RA
TS score finger	2.47	1.71	2.19	2.14	2.11	2.00	
TS score finger	2.58	2.17	2.72	1.69	1.83	2.73	
TS score shoulder	1.95	1.51	1.12	1.54	1.17	1.76	
TS score shoulder	0.89	2.89	1.22	1.83	1.22	1.99	CFS < CON
Cuff pressure threshold	100.26	32.34	149.37	63.16	163.33	50.06	CFS < CON = RA
Cuff pressure threshold	102.50	50.30	167.50	84.97	179.72	64.55	CFS < CON = RA
VNRS ischaemic cuff	5.74	1.88	4.50	2.39	3.75	2.32	CFS < CON
VNRS ischaemic cuff	5.56	2.23	4.59	2.32	3.78	2.37	CFS < CON
Cuff pressure at VNRS = 3	60.79	39.97	109.06	65.10	136.94	57.12	CFS < CON = RA
Cuff pressure at VNRS = 3	62.22	45.90	105.63	50.49	153.89	72.79	CFS < CON
CPM score finger	-0.05	1.39	0.56	1.14	0.47	1.40	
CPM score finger	0.06	0.94	0.72	1.44	-0.11	1.13	
CPM score shoulder	0.79	1.36	0.91	1.07	0.58	0.97	
CPM score shoulder	-0.22	2.21	0.13	1.04	0.42	1.29	

(*CFS/FM measurements under placebo: n = 18; TS = Temporal summation, CPM = Conditioned Pain Modulation)

Table 2. *Pressure pain thresholds (PPT's) under acetaminophen and placebo.*

		Acetaminophen		Placebo		Significant differences	Cohen's d effect size
		Mean	SD	Mean	SD		
CFS	finger	5.89	2.27	5.80	2.49	0.000	0.038
	shoulder	2.00	1.28	1.83	0.82	0.001	0.157
RA	finger	6.63	2.70	6.73	3.09	0.007	-0.034
	shoulder	4.13	2.36	4.19	3.04	0.000	-0.022
CON	finger	8.50	1.86	9.53	2.50	0.081	-0.467
	shoulder	4.89	1.94	5.19	2.07	0.000	-0.150

significantly lower compared to the controls and RA patients.

A lower TS score was only observed at the shoulder in CFS/FM patients compared to the healthy controls.

Comparison of Characteristics under Acetaminophen

Under acetaminophen the same differences were observed, regardless of a similar TS score at the shoulder under this condition.

Comparison Acetaminophen versus Placebo Condition

PPT's

It seems that acetaminophen has significant effects on PPT's in the 3 groups, but only in the CFS group did it lead to a significant increase of the PPT, as shown in Table 2. In the other 2 groups a decrease was observed.

Manifestation of TS

Under placebo, the findings are not consistent

and opposite in the shoulder compared to the finger (Figs. 2A and 2B). For the finger there is a significant interaction effect (P = 0.039), with increased TS score during CPM (ischaemic cuff) in the healthy controls and reduced TS scores during CPM in the patient groups.

As presented in Figs. 3A and 3B, under acetamino-phen TS during CPM decreased most of the time in the 3 groups, suggesting a normal CPM function.

For the shoulder, there is a significant main effect for time (P = 0.002).

Temporal summation is always the highest in CFS/FM patients, although the differences are not significant.
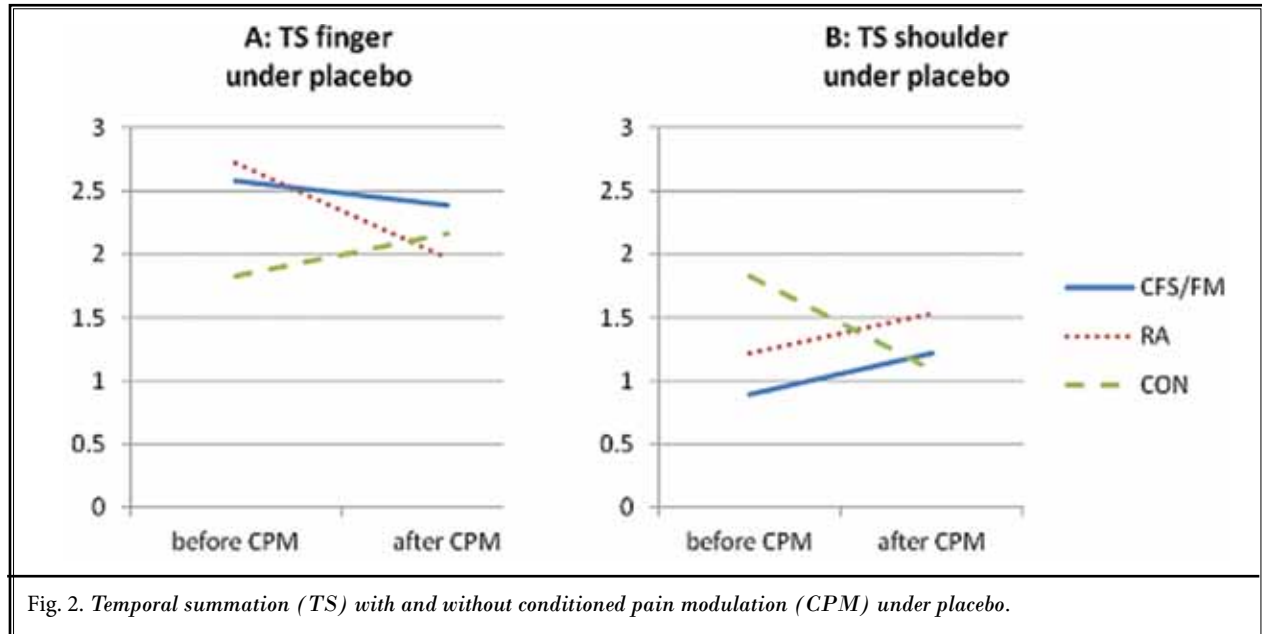

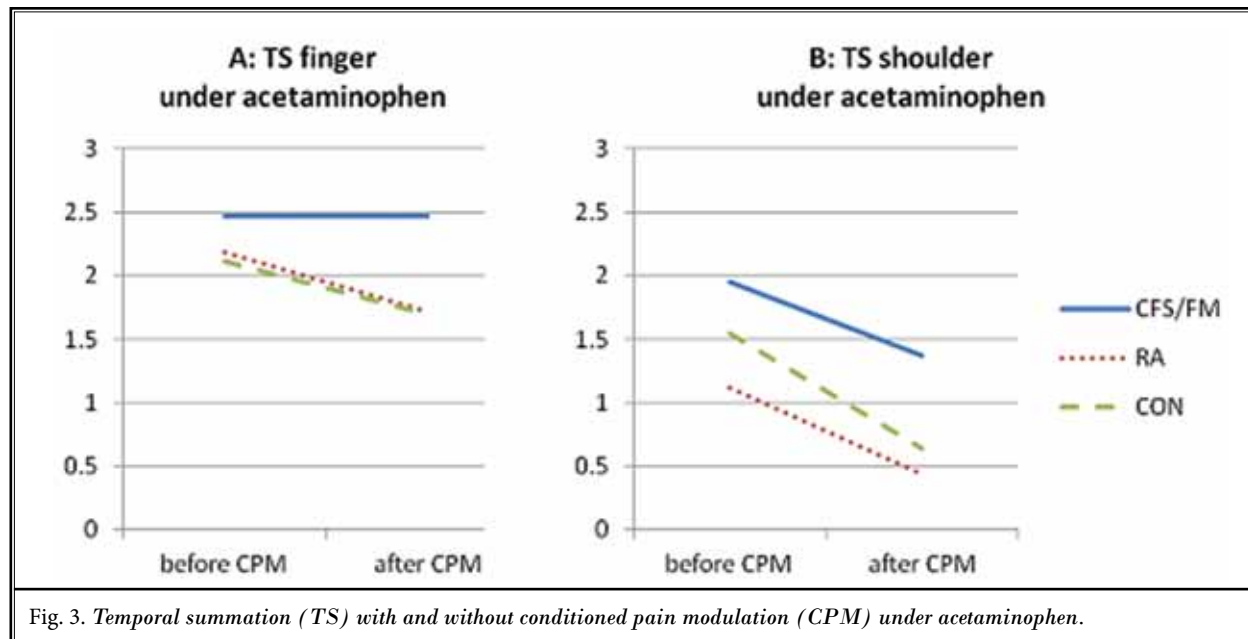Fig. 2. *Temporal summation (TS) with and without conditioned pain modulation (CPM) under placebo.*

Fig. 3. *Temporal summation (TS) with and without conditioned pain modulation (CPM) under acetaminophen.*

Efficacy CPM

For the shoulder CPM was consistently better under acetaminophen. For the RA group the difference was significant (P = .026) (Fig. 4).

For the finger, only the control subjects presented better CPM function with acetaminophen. In the RA patients and the CFS/FM patients there was not a great difference between the CPM scores under acetaminophen or placebo.

In general, CPM scores are lower (not significant) in CFS/FM patients.

Efficacy Blinding

Twenty-five of the 52 patients judged their allocation correctly, while the assessor judged 28 of the 52 case correctly. Both figures approach 50%, indicating successful blinding.

DISCUSSION

The goal of the present study was to evaluate TS and CPM under placebo and acetaminophen condition in healthy controls and 2 different chronic pain populations (i.e., patients with RA and patients with CFS/FM), and to compare the different groups and conditions.

Patients with CFS/FM presented widespread hyperalgesia, as evidenced by significantly lower PPT's and cuff pressures, and higher VNRS scores compared to healthy controls and even to the patients with RA for some variables. Patients with RA were more similar

to the healthy controls despite the PPT at the finger, suggesting primary hyperalgesia (peripheral sensitization) rather than widespread hyperalgesia as a sign for central sensitization. Furthermore, it is known that RA frequently affects finger joints, and persistent synovitis is believed to cause not only bone destruction but also various deformities of the fingers in the long run.

Although CFS/FM patients presented overall higher TS scores and lower CPM scores compared to the control group and the RA group, there were no significant differences between the 3 groups under placebo and acetaminophen. However, the study was not designed to compare the differences in TS and CPM between the various groups. Hence, it would be premature to make conclusions regarding TS and CPM differences between groups. In addition, both conditions might be influenced by acetaminophen, expectations, placebo effect, etc. Since it is known that the modulation of pain by expectations is mediated by top-down endogenous pain modulatory systems affecting nociceptive signal processing at the earliest stage of the central nervous system (29), the placebo effect may have influenced the results (cfr. the efficacy of the blinding). Therefore, we cannot draw conclusions about the function of CPM in CFS/FM and RA, based on the present results.

Regarding the influence of acetaminophen, PPT's slightly increase in CFS/FM patients and decrease in patients with RA and healthy controls. The differences are however very small (cfr. effect sizes), as could be
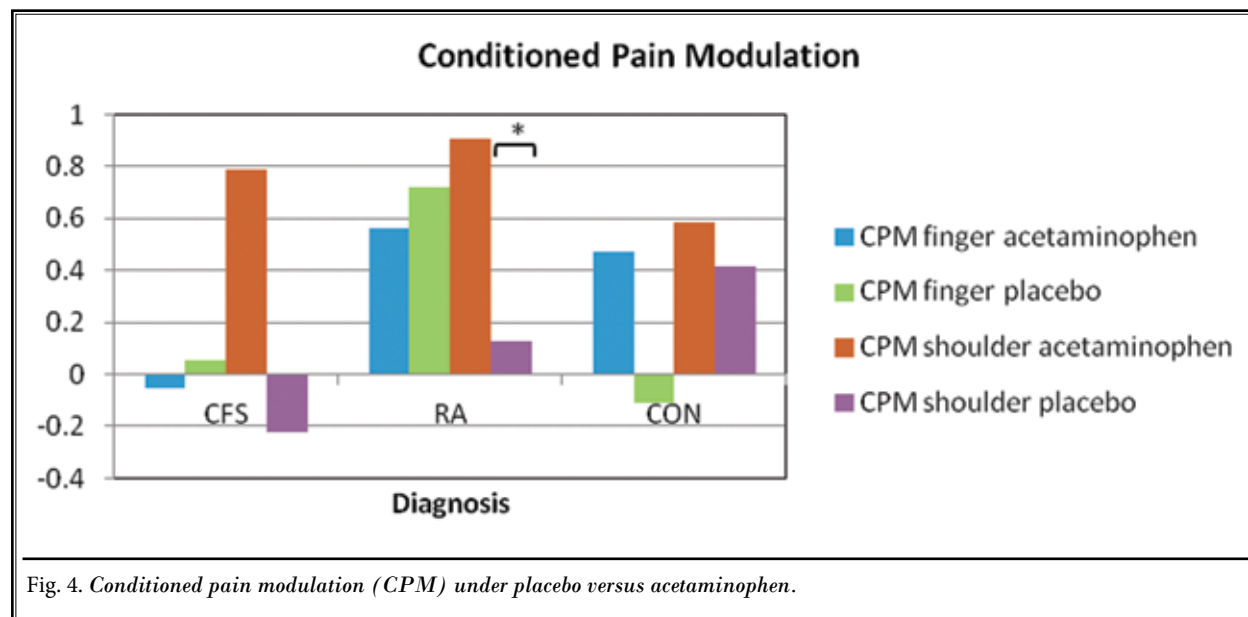

Fig. 4. *Conditioned pain modulation (CPM) under placebo versus acetaminophen.*

expected based on past studies that could not find an effect of acetaminophen on pain thresholds (30,31). Furthermore, it is not known what difference in pain threshold can be called clinically significant. Graphs clearly indicate that acetaminophen reduces the efficacy of TS in all groups, leading to consistent lowering of the TS scores (significant for the shoulder). Similarly, for the shoulder CPM seems to be more efficient under acetaminophen, while the findings are inconsistent for the finger.

The present study findings indicate that acetaminophen has positive effects in suppressing TS of pain. The supporting role of acetaminophen in CPM is however still unclear because of inconsistent results for the shoulder and finger. The observation that CPM was activated by acetaminophen if evaluated at the shoulder, but not at the finger, may be the consequence of the fact that after repeated pressure stimuli, the finger became highly sensitive in all participants. TS scores are overall higher at the finger compared to the shoulder. The majority of participants still reported after-sensations of pain due to the first TS sequence, when the second TS sequence (during the conditioning cuff inflation) was started. This way, the second TS sequence did not start at a normal baseline, as was the case for the shoulder.

On the other hand, it is known that pain originating in deep soft tissue (like the trapezius muscle) influences central pain processing systems more than superficial tissue (like the finger) (32). This could explain why CPM scores are generally higher at the shoulder compared to the finger and why the findings at the finger are inconsistent.

Nevertheless, acetaminophen is efficacious in enhancing CPM effect in healthy controls. In RA patients and CFS/FM patients, the additional value of acetaminophen is less clear, suggesting that other pathways may require stimulation to obtain better endogenous pain inhibition. An explanation may be found in the pathways that are modulated by acetaminophen. Possibly, the serotonergic pathways are not important players in the (dis)functioning of CPM. They may contribute partly, but other pathways may be of greater importance, like for example, the opioid pathways. The latter hypothesis is supported by the findings of King et al (33), who reported that the inhibitory effect of CPM is reduced with naltrexone, suggesting at least partial dependence of inhibition on endogenous opioids. It would therefore be interesting to study the opposite, namely the modulation of the function of CPM in chronic pain patients by opioid agonists.

The observation that PPT's increase in CFS/FM patients under acetaminophen may indicate that acetaminophen can be useful for these patients in suppressing pain, but are less likely to fully support endogenous pain inhibition. The therapeutic approach may therefore require modulation of multiple pathways. Further research is however warranted to answer these questions.

Finally, it is quite possible that the procedure used in this study lead to peripheral sensitization of the finger, since many participants, both patients and controls, complained of pain and after-sensations at the finger up to 24 hours after the test (and not at the shoulder). The fact that acetaminophen primarily acts centrally by reinforcing descending inhibitory pathways (19) may explain the lack of a definite effect of acetaminophen on CPM at the finger.

The present study should be interpreted in the light of some limitations, opening doors for future studies. Although it was interesting to observe such differences between finger and shoulder, probably reflecting the differences between deep and superficial tissue and between more peripheral problems versus central abnormalities, future research should reflect about using the finger in this protocol to assess CPM. Although this may be a limitation, in the meantime it may be interesting for the present study in which a disease predominantly considered as a peripheral condition (RA) is compared to a central disfunctioning syndrome (CFS/FM).

Additionally, it remains a question how to assess CPM: mechanical stimuli, thermal stimulation, or chemical?

Finally, to preclude interference of the entry pharmacotherapy of the patients, patients had to refrain from antidepressants and other medications for 2 weeks and pain medication from WHO step 1 for 48 hours prior to study participation. This was a sufficient wash-out period, based on the literature study of Smith and Barkin (34), but may have led to withdrawal phenomena or a temporary pain exacerbation and to exclusion of those patients who could not stop their medication.

To the best of our knowledge, this is the first study comparing TS and CPM between different populations and under placebo versus acetaminophen condition. The findings suggest that serotonergic pathways play a role in TS and CPM, but probably only for deeper tissues, and it is plausible that other pathways even contribute to the (dis)function of central pain process-

ing. It is clear that this domain remains a complex issue and that far more research is warranted to unravel the mechanism of endogenous pain inhibition and to unravel the possible disfunction. Furthermore, practical and clinical useful measures for endogenous pain inhibition are required.

CONCLUSION

This cross-over RCT showed that acetaminophen may partly support conditioned pain, but that other contributors than serotonergic pathways should be identified.

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