in vivo *25*: 1019-1026 (2011)

Serotonergic Descending Inhibition in Chronic Pain: Design, Preliminary Results and Early Cessation of a Randomized Controlled Trial

MIRA MEEUS[1,2], KELLY ICKMANS[1,2], LUC S DE CLERCK[3], GRETA MOORKENS[4], GUY HANS[5], SOFIE GROSEMANS[5] and JO NIJS[1,2,6]

[1]*Department of Human Physiology, Faculty of Physical Education and Physiotherapy, Vrije Universiteit Brussel, Belgium;*
[2]*Division of Musculoskeletal Physiotherapy, Higher Institute of Physiotherapy, Department of Health Care Sciences, Artesis University College Antwerp, Belgium;*
[3]*Department of Immunology, Allergy and Rheumatology, University of Antwerp, Belgium;*
[4]*Department of Internal Medicine, and*
[5]*Multidisciplinary Pain Center, University Hospital Antwerp, Belgium;*
[6]*Department of Rehabilitation and Physiotherapy, University Hospital Brussels, Belgium*

Abstract. *Aim: We examined whether activation of serotonergic descending pathways improves pain inhibition during exercise in patients with chronic fatigue syndrome (CFS) and comorbid fibromyalgia (FM) in comparison with rheumatoid arthritis (RA) and sedentary, healthy controls in a double-blind randomized controlled trial with cross-over design. Patients and Methods: Three female CFS/FM patients, one female RA patient and two healthy women were randomly allocated to the experimental group (2 ml of citalopram intravenously) or the placebo group (2 ml of 0.9% NaCl intravenously). Participants performed a submaximal exercise protocol, preceded and followed by an assessment of endogenous pain inhibition. Seven days later, groups were crossed over. Results: Significant side-effects were observed in all, but one participant immediately after intravenous administration of citalopram. One CFS/FM patient withdrew because of severe post-exertional malaise. Conclusion: It was decided that proceeding with the study would be unethical. No conclusion could be made regarding pain inhibition during exercise in CFS/FM compared to RA and controls.*

Chronic pain is the most debilitating symptom in many medical conditions, including rheumatoid arthritis (RA) and fibromyalgia (FM). 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 (1), a role attributed to the 'diffuse noxious inhibitory controls (DNIC)' phenomenon (2). In cases of chronic pain and central sensitization, the descending pain-inhibitory pathways, including DNIC, are aberrant (3, 4). Besides DNIC, another mechanism is characteristic of central sensitization: enhanced temporal summation of second pain or 'wind-up'. 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 (5, 6).

Malfunctioning of central pain-inhibitory pathways in people with chronic pain becomes particularly apparent to clinicians during physical activity and exercise interventions: both isometric and aerobic exercise activates endogenous opioid and adrenergic pain-inhibitory mechanisms in healthy individuals, while it increases experimental pain ratings in patients with central sensitization (7, 8). It remains, however, unclear whether descending serotonergic pathways are responsible. Unraveling the mechanisms responsible for impaired pain inhibition in response to exercise in people with chronic pain and central sensitization might be crucial in developing appropriate drug treatments to prevent post-exertional malaise. Whilst endogenous opioid and adrenergic pain-inhibitory mechanisms appear to account for activation of pain inhibition during exercise in healthy individuals (9, 10), direct evidence is lacking.

Correspondence to: Mira Meeus, Department of Human Physiology, Faculty of Physical Education and Physiotherapy, Vrije Universiteit Brussel, Building L-Mfys, Pleinlaan 2, 1050 Brussels, Belgium. Tel: +32 485582114, e-mail: Mira.Meeus@vub.ac.be

Key Words: Sensitization, chronic fatigue syndrome, fibromyalgia, rheumatoid arthritis, citalopram.

Likewise, DNIC is aberrant in people with central sensitization, but the precise mechanism remains to be revealed. It is suggested that DNIC implies systems that are opioid-mediated (11). Studies examining the nature of pain-inhibitory systems activated by the spatial summation model in patients with chronic pain are essentially lacking. Therefore, the question remains whether impaired DNIC in patients with chronic pain and central sensitization is due to malfunctioning of opioid-mediated pain inhibition.

The present study aimed at examining the contribution of endogenous opioid pain-inhibitory mechanisms during exercise in two chronic pain populations: those with RA and those suffering chronic fatigue syndrome (CFS) and comorbid FM. We modulated endogenous opioid and serotonergic pain-inhibitory mechanisms during exercises by using selective serotonin reuptake inhibitor (SSRI) during the DNIC and temporal summation (TS) model in response to exercise. Indeed, SSRIs activate serotonergic descending pathways that recruit, in part, opioid peptide-containing interneurons of the dorsal horn (12). The study aimed at examining whether activation of serotonergic descending pathways improves pain inhibition during exercise in patients with RA and those with CFS/FM.

Patients and Methods

This was a double-blinded randomized controlled trial with cross-over design. 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).

Participants. The present study aimed at enrolling two chronic pain populations: those with RA and those with a typical central sensitization image *i.e.* individuals fulfilling the criteria for both CFS and primary FM. Furthermore, healthy sedentary pain-free controls were included. Each study participant was female and aged between 18 and 65 years. The CFS/FM group complied with the diagnostic criteria for FM as defined by the American College of Rheumatology (13) and the Centre of Disease Control criteria for CFS (14). At the time of study participation, healthy controls did not have any pain complaints. Sedentary was defined as having a sedentary job and performing <3 h moderate physical activity/week (15). Participants were not pregnant, <1 year postnatal, and were asked to stop anti-depressive medication and other analgesic medication two 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.

Based on an *a priori* power analysis, we aimed at enrolling three groups of subjects: 20 patients with FM and CFS, 20 patients with RA, and 30 healthy sedentary pain-free controls. Sample size was calculated based on a power analysis (0.80), based on our previous study on spatial summation (3) and a study of temporal summation in FM patients (4).

Procedure. In order to evaluate whether activation of serotonergic descending pathways improved pain inhibition during exercise, patients were allocated to a placebo group or an experimental group that received intravenous citalopram, an SSRI. The experiment started with an evaluation of the functioning of endogenous pain inhibition, as presented in Figure 1. After this evaluation, participants performed a standardized submaximal exercise protocol, followed again by the assessment of the efficacy of endogenous pain inhibition. This protocol was repeated in cross-over design 7 days later, accounting for the long half-life of citalopram and for the eventual fatigue and pain complaints of the patients.

Endogenous pain inhibition. The efficacy of endogenous pain inhibition was assessed by a procedure of TS and spatial summation of noxious stimuli, as described by Cathcart *et al*. (16). 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, UK) at 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 trapezius belly of the right arm. The participants were asked to rate the intensity and unpleasantness of the pain of the 1st, 5th and 10th pulse on a verbal numerical rating scale (0=no pain to 10=worst possible pain). DNIC was assessed by replicating the TS assessment associated with a conditioning stimulus for eliciting DNIC. The conditioning stimulus was an occlusion cuff at the left arm inflated to a painful intensity and maintained at that level while TS was elicited. This procedure is explained in depth elsewhere and seemed reliable (16). The outcome measure for TS is the difference between the 10th and the 1st pain rating score before cuff inflation. The measure for DNIC is the difference between the 10th pain rating score before occlusion and the 10th during occlusion. This means that 8 TS scores and 4 DNIC scores were obtained per test site (finger and shoulder) for each participant.

Submaximal exercise test. The submaximal exercise protocol consisted of the exercise protocol of the Aerobic Power Index Test (using an increase of 25 W every minute). The Aerobic Power Index Test is a reliable and valid submaximal exercise testing protocol for chronic pain patients and healthy individuals (17). Participants had to cycle (60 r/s) on an electromagnetically braked ergometer (Gymna Ergofit Cycle 407 MED; Gymna, Bilzen, Belgium) until submaximal heart rate (75% of 220−age bpm).

Statistical analysis. All data were analyzed using the Statistical Package for Social Sciences 16.0© for Windows (SPSS Inc., Chicago, IL, USA). Given the small sample, non-parametric statistics were used. Descriptive data are presented as medians and ranges, if possible. Comparisons between groups were performed with Kruskal-Wallis tests. For comparison of TS within groups, we compared TS1 with TS3 (before and after exercise with placebo), TS1 with TS5 (before exercise placebo *versus* SSRI), and TS5 with TS7 (before and after exercise with SSRI) with the Wilcoxon signed ranks test.

For comparison of DNIC within groups we compared DNIC1 with DNIC2 (before and after exercise with placebo), DNIC1 and DNIC3 (before exercise placebo *versus* SSRI), and DNIC3 with DNIC4 (before and after exercise with SSRI) with the Wilcoxon signed ranks test.

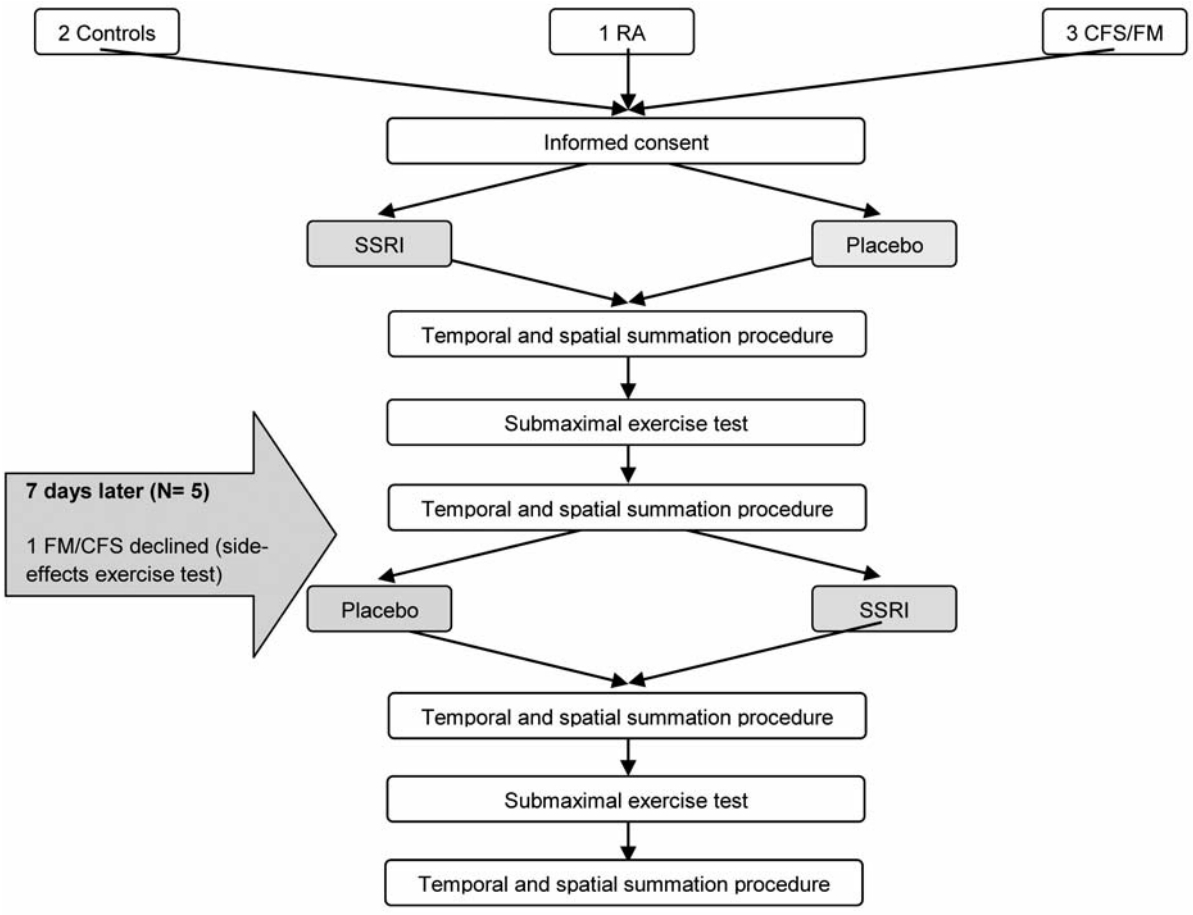

Figure 1. *Flow diagram of the study.*

In this way, we analyzed how pain inhibition reacts to exercise in different patients and if pain inhibition is altered in response to experimental manipulation with SSRI. This pilot study allowed us to determine, for example, whether pain inhibition is deficient and opioid-mediated.

Results

Three CFS/FM patients, 1 RA patient and 2 healthy controls participated in this study. The study was prematurely discontinued due to the intense side-effects of intravenous SSRI. The demographical variables of the participants are presented in Table I. Participant 2 did not complete the study because of an exacerbation of her symptoms after the first exercise test.

Table I. *Demographical variables of participants (all female).*

	Diagnosis	Age (years)	Illness duration (years)	Professional situation
1	CFS/FM	47	1.5	Not active
2	CFS/FM	54	10	Not active
3	CFS/FM	48	15	Not active
4	RA	49	8	Part-time
5	CON	24	0	Full-time
6	CON	58	0	Retired

CFS/FM: Chronic fatigue syndrome and comorbid fibromyalgia; RA: rheumatoid arthritis; CON: controls.

Pain thresholds. Pain thresholds were not significantly different between the three groups or different within the groups. Results are presented in Table II.

Temporal summation. Comparing the three groups for TS efficacy, no significant difference was found (p-value ranging between 0.174 and 0.823). Within the groups, no differences were revealed (p-value ranging between 0.157 and 1.000). Evolution of TS is presented in Figure 2.

DNIC. There was no significant difference for DNIC between CFS/FM, RA patients and healthy controls, as

Table II. *Pressure pain thresholds (PPT) for the three groups (median and range).*

PPT	CFS/FM N=3 or N=2 (PPT2)	RA N=1	CON N=2	Kruskal-Wallis *p*-value
Finger 1	8.95 (5.00-10.00)	6.30	6.93 (6.00-8.00)	0.807
Finger 2	6.40 (3.20-9.60)	8.10	7.58 (7.00-8.10)	0.924
Wilcoxon *p*-value	0.180	/	0.180	
Shoulder 1	2.20 (2.10-3.60)	3.15	3.28 (3.00-3.50)	0.807
Shoulder 2	2.28 (1.40-3.20)	4.50	3.88 (3.80-3.90)	0.165
Wilcoxon *p*-value	0.180	/	0.180	

CFS/FM: Chronic fatigue syndrome and comorbid fibromyalgia; RA: rheumatoid arthritis; CON: controls.

Table III. *Values for diffuse noxious inhibitory controls (DNIC) for the three groups (median and range).*

DNIC	CFS/FM N=3 or N=2 (DNIC 3&4)	RA N=1	CON N=2	Kruskal-Wallis *p*-value
Finger 1	−1.00 (−2.00-−1.00)	–0.50	0.25 (0.00-1.00)	0.122
Finger 2	−0.50 (−1.00-1.00)	1.00	−0.25 (−1.00-0.00)	0.454
Finger 3	0.00 (0.00-0.00)	1.50	−0.50 (−1.00-0.00)	0.223
Finger 4	−0.50 (−1.00-0.00)	0.00	0.00 (−1.00-1.00)	0.823
Shoulder 1	0.00 (0.00-1.00)	0.00	1.33 (0.00-3.00)	0.885
Shoulder 2	−0.83 (−2.00-−1.00)	1.00	−1.17 (−2.00-0.00)	0.343
Shoulder 3	−1.00 (0.33-−2.33)	1.00	−5.00 (−2.00-1.00)	0.398
Shoulder 4	1.00 (0.67-1.33)	0.00	0.42 (−0.16-1.00)	0.497

CFS/FM: Chronic fatigue syndrome and comorbid fibromyalgia; RA: rheumatoid arthritis; CON: controls.

presented in Table III. Also within the groups no differences could be revealed (*p*-value ranging between 0.180 and 0.655). Evolution of DNIC is presented in Figure 3.

Side-effects. One CFS/FM patient withdrew after the first study day because of severe post-exertional malaise that lasted until one week later. She had received a placebo.

Significant side-effects were observed in all but one participant immediately after intravenous administration of the SSRI. Two CFS/FM patients felt extremely nauseous and therefore received an antiemetic drug (Litican) *via* intravenous injection. Nausea persisted until one hour after administration of citalopram. The RA patient indicated nausea and dizziness immediately after administration of the SSRI. These side-effects disappeared spontaneously after 30 min. One healthy control was the only participant who did not show any severe adverse events. This person only complained of somnolence after the drug injection. The second control who participated in this study showed extreme nausea immediately after administration of citalopram. This person vomited several times and although an antiemetic agent (Litican) was administered intravenously, nausea persisted for 36 h.

Discussion

Although the aim of the present study was to evaluate whether the administration of the SSRI citalopram could improve descending pain inhibition during exercise, we had to stop the study after inclusion of only 6 participants because of intense side-effects. One CFS/FM patient experienced serious symptom exacerbation due to the exercise test (under placebo), and four other participants (patients and controls) suffered intense side-effects immediately after the administration of the SSRI which lasted for up to 36 h. Given the severe side-effects observed, it was decided that proceeding with the study in its present form would be unethical. The risks were too high, especially because patients were allowed to return home afterwards.

Regarding endogenous pain inhibition after exercise and the effect of citalopram on descending pain inhibition, we cannot draw conclusions based on this small sample. We were unable to reveal any significant difference between the three groups, before and after cuff occlusion, before and after exercise, with placebo or citalopram, etc. The sample is too small and the findings are not consistent. In addition, study results regarding pain inhibition may be biased due to the

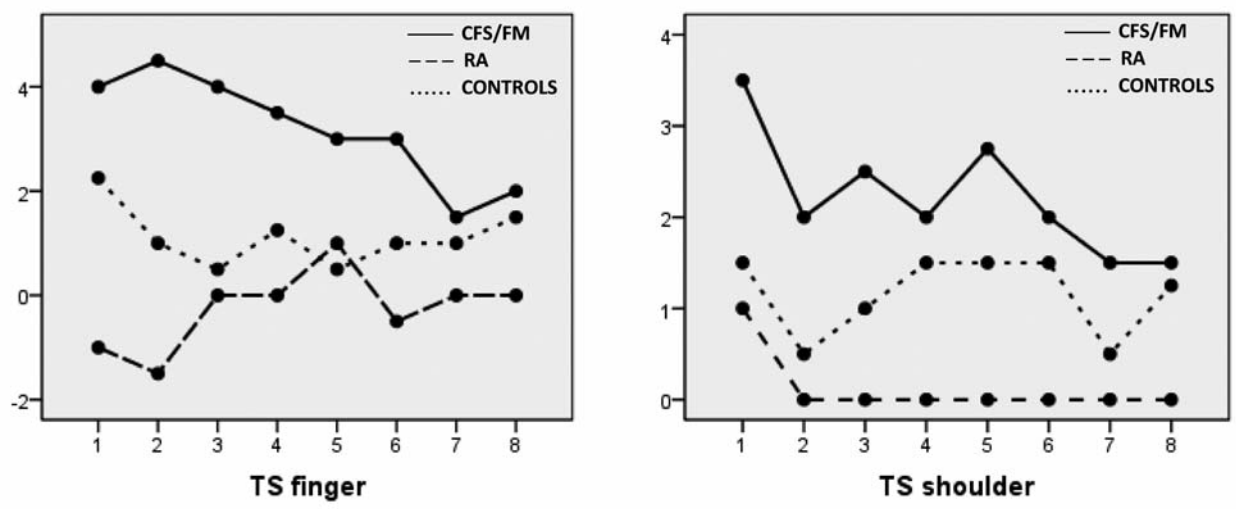

Figure 2. *Evolution of temporal summation (TS). TS value=10th pain – 1th pain score; TS 1=Placebo, before occlusion, before exercise; TS 2=Placebo, after occlusion, before exercise; TS 3=Placebo, before occlusion, after exercise; TS 4=Placebo, before occlusion, after exercise; TS 5=SSRI, before occlusion, before exercise; TS 6=SSRI, after occlusion, before exercise; TS 7=SSRI, before occlusion, after exercise; TS 8=SSRI, before occlusion, after exercise.*

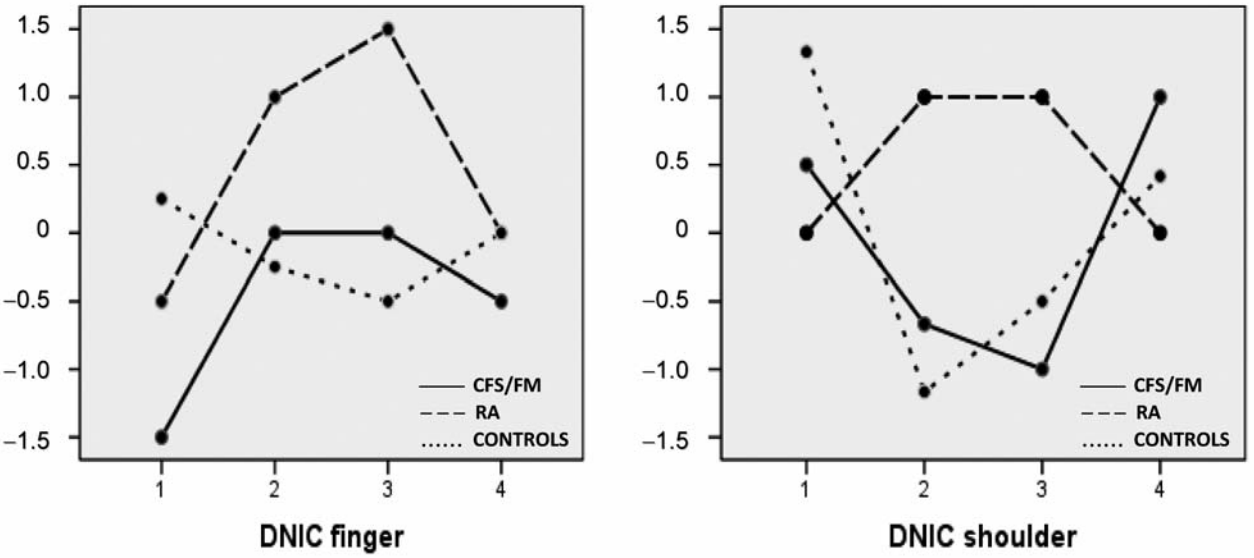

Figure 3. *Evolution of diffuse noxious inhibitory controls (DNIC). DNIC value=10th pain score before cuff occlusion – 10th pain score after cuff occlusion; DNIC 1=Placebo, before exercise; DNIC 3=SSRI, before exercise; DNIC 2=Placebo, after exercise; DNIC 4=SSRI, after exercise.*

intense side-effects experienced. Moreover, at baseline, no significant differences were found between patients and controls for the degree of wind-up and the efficacy of DNIC.

Nevertheless, we are convinced of the relevance of reporting these findings, particularly as regards the claimed link between CFS and depression or anxiety. Although comorbid depression is a common emotional response to any chronic illness, some patients with CFS are not clinically depressed. These patients are poorly served when depression is the only diagnosis they are offered. Comorbid depression in CFS has been perceived as evidence that CFS is an atypical manifestation of depression. Ongoing research into specific brain, hormonal, and immunologic abnormalities consistent with CFS will undoubtedly continue to shed new

light onto the aetiology of this frustrating illness, with possibilities for finding diagnostic markers that can be used to more easily identify CFS.

Although the debate about CFS as a medical or psychiatric condition will likely continue, it is not likely that depression will be proven to be the primary cause (18). Depressed or anxious patients do not respond this way to SSRIs as observed in the present study, otherwise the drug would not be licensed for their use. Depressive patients usually benefit from antidepressants, while the literature concerning the effect of SSRIs for chronic pain in non-depressed patients is controversial. The benefits of SSRIs compared to placebo in non-depressed patients are controversial and likely to be small (19, 20). Moreover, side-effects are frequently seen in non-depressed patients (21, 22). Different studies focused on the citalopram challenge test. During this test, an acute oral or intravenous administration of citalopram (10 or 20 mg) is used to evaluate central serotonin activity and function *in vivo* (21, 22). This SSRI activates serotonergic descending pathways that recruit, in part, opioid peptide-containing interneurons of the dorsal horn and it is the most selective serotonin reuptake inhibitor that potentiates serotonergic transmission by selectively blocking serotonin reuptake (23). Variability in acute responses to serotonin challenge probes, determined using either neuro-endocrine responses or functional imaging, can be used to measure variability in the serotonergic system (24, 25).

In psychiatric diseases with a known altered function of the serotonin system, changes in the neuroendocrine response to serotonergic stimulation have been shown. For instance in major depression, a blunted hormonal response has repeatedly been reported (26). In healthy individuals, citalopram challenge tests resulted in normal neuro-endocrine responses: a prompt increase in prolactin and cortisol levels, reaching a maximum peak level 30 min after the start of the administration. In addition, side-effects appeared within 15-30 min after citalopram administration. Significant increases in nausea and side-effects were observed in healthy volunteers compared to placebo or compared to depressed individuals (21). This may explain why our study participants, not suffering major depressive disorders, presented intense side-effects. These findings emphasize the fact that while CFS/FM and depression share symptoms and may coexist, it is not likely that depression is the primary cause for CFS/FM. Considering our study, many and intense side-effects were reported, suggesting that the participants reacted seriously to the acute administration. CFS/FM patients possibly do not show a blunted serotonin response, but this hypothesis requires further research, as do possible treatment approaches.

Of course, we should be careful in formulating hypotheses and conclusions based on the present small sample. The study was stopped because of the serious side-effects. We thought it was unethical to continue the study while the goal was to assess the possible benefit of citalopram on endogenous pain inhibition at rest and during exercise in CFS/FM and RA patients. Besides the small sample, blinding was not efficacious because of the side-effects. Both participants and researcher became unblinded during the procedure.

Despite the restrictions of this study, it opens new perspectives for further research into serotonergic activity in different non-depressed chronic pain patients. While a body of literature on chronic pain is currently available, only few studies have made direct comparisons between different chronic pain conditions. Comparison of various chronic pain disorders is crucial for unravelling the differences and similarities in the nature of chronic pain, especially to steer treatment. In the present study for example, a chronic pain condition with a joint pathology (RA) was compared with chronic pain in patients without peripheral abnormalities but with evidence for central sensitization (*i.e.* CFS/FM).

Besides the finding that acute intravenous administration of citalopram induced intense side-effects in four out of the five participants, the present study did not reveal any significant differences in TS and DNIC (before and after exercise) between the different groups or any significant effect of citalopram on pain inhibition. Further study is required to unravel pain inhibition and serotonergic activity in these chronic pain patients.

Acknowledgements

The study was funded by ME Research UK. Mira Meeus is a postdoctoral research fellow of the Research Foundation Flanders (FWO). Kelly Ickmans is a research fellow of ME Research UK, a national charity funding biomedical research into myalgic encephalomyelitis/chronic fatigue syndrome.

References

1 Woolf CJ and Salter MW: Neuronal plasticity: increasing the gain in pain. Science *288*: 1765-1769, 2000.

2 Le Bars D and Villanueva L: Electrophysiological evidence for the activation of descending inhibitory controls by nociceptive afferent pathways. Prog Brain Res *77*: 275-299, 1988.

3 Meeus M, Nijs J, Van de Wauwer N, Toeback L and Truijen S: Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: An experimental study. Pain *139*: 439-448, 2008.

4 Staud R, Vierck CJ, Cannon RL, Mauderli AP and Price DD: Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. Pain *91*: 165-175, 2001.

5 Staud R, Craggs JG, Robinson ME, Perlstein WM and Price DD: Brain activity related to temporal summation of C-fiber evoked pain. Pain *129*: 130-142, 2007.

6 Meeus M and Nijs J: Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. Clin Rheumatol *26*: 465-473, 2007.

7 Whiteside A, Hansen S and Chaudhuri A: Exercise lowers pain threshold in chronic fatigue syndrome. Pain *109*: 497-499, 2004.
8 Staud R, Robinson ME and Price DD: Isometric exercise has opposite effects on central pain mechanisms in fibromyalgia patients compared to normal controls. Pain *118*: 176-184, 2005.
9 Koltyn KF and Arbogast RW: Perception of pain after resistance exercise. Br J Sports Med *32*: 20-24, 1998.
10 Hoffman MD, Shepanski MA, Mackenzie SP and Clifford PS: Experimentally induced pain perception is acutely reduced by aerobic exercise in people with chronic low back pain. J Rehabil Res Dev *42*: 183-190, 2005.
11 Julien N and Marchand S: Endogenous pain inhibitory systems activated by spatial summation are opioid-mediated. Neurosci Lett *401*: 256-260, 2006.
12 Basbaum AI and Fields HL: Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annu Rev Neurosci *7*: 309-338, 1984.
13 Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB and Yunus MB: The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) *62*: 600-610, 2010.
14 Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG and Komaroff A: The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med *121*: 953-959, 1994.
15 Bernstein MS, Morabia A and Sloutskis D: Definition and prevalence of sedentarism in an urban population. Am J Public Health *89*: 862-867, 1999.
16 Cathcart S, Winefield AH, Rolan P and Lushington K: Reliability of temporal summation and diffuse noxious inhibitory control. Pain Res Manag *14*: 433-438, 2009.
17 Wallman KE, Morton AR, Goodman C and Grove R: Physiological responses during a submaximal cycle test in chronic fatigue syndrome. Med Sci Sports Exerc *36*: 1682-1688, 2004.
18 Erdman KM: How biological abnormalities separate CFS from depression. Journal of the American Academy of Physician Assistants *21*: 19-23, 2008.
19 Ladabaum U, Sharabidze A, Levin TR, Zhao WK, Chung E, Bacchetti P, Jin C, Grimes B and Pepin CJ: Citalopram provides little or no benefit in nondepressed patients with irritable bowel syndrome. Clin Gastroenterol Hepatol *8*: 42-48 e41, 2010.
20 Otto M, Bach FW, Jensen TS, Brosen K and Sindrup SH: Escitalopram in painful polyneuropathy: a randomized, placebo-controlled, cross-over trial. Pain *139*: 275-283, 2008.
21 Kapitany T, Schindl M, Schindler SD, Hesselmann B, Fureder T, Barnas C, Sieghart W and Kasper S: The citalopram challenge test in patients with major depression and in healthy controls. Psychiatry Res *88*: 75-88, 1999.
22 Seifritz E, Baumann P, Muller MJ, Annen O, Amey M, Hemmeter U, Hatzinger M, Chardon F and Holsboer-Trachsler E: Neuroendocrine effects of a 20-mg citalopram infusion in healthy males. A placebo-controlled evaluation of citalopram as 5-HT function probe. Neuropsychopharmacology *14*: 253-263, 1996.
23 Willets J, Lippa A and Beer B: Clinical development of citalopram. J Clin Psychopharmacol *19*: 36S-46S, 1999.
24 Smith GS, Kramer E, Hermann CR, Goldberg S, Ma Y, Dhawan V, Barnes A, Chaly T, Belakhleff A, Laghrissi-Thode F, Greenwald B, Eidelberg D and Pollock BG: Acute and chronic effects of citalopram on cerebral glucose metabolism in geriatric depression. Am J Geriatr Psychiatry *10*: 715-723, 2002.
25 Smith GS, Ma Y, Dhawan V, Gunduz H, Carbon M, Kirshner M, Larson J, Chaly T, Belakhleff A, Kramer E, Greenwald B, Kane JM, Laghrissi-Thode F, Pollock BG and Eidelber D: Serotonin modulation of cerebral glucose metabolism measured with positron emission tomography (PET) in human subjects. Synapse *45*: 105-112, 2002.
26 Heninger GR, Charney DS and Sternberg DE: Serotonergic function in depression. Prolactin response to intravenous tryptophan in depressed patients and healthy subjects. Arch Gen Psychiatry *41*: 398-402, 1984.

Received June 29, 2011
Revised August 5, 2011
Accepted August 8, 2011