



**Karolinska
Institutet**

Department of Clinical Neuroscience

Implications of autonomic nervous system and central inflammatory parameters for the perception of pain in fibromyalgia patients

AKADEMISK AVHANDLING

Som för avläggande av medicine doktorexamen vid Karolinska Institutet offentlig försvaras i Hillertsalen, Retzius väg 8, Stockholm.

Fredagen den 9 November, 2012, kl 13.00

av

Diana Kadetoff

Huvudhandledare:

Docent Eva Kosek
Dept. Clinical Neuroscience
Karolinska Institute

Bihandledare:

Prof. Martin Ingvar
Dept Clinical Neuroscience
Karolinska Institute

Fakultetsopponent:

Prof. Torsten Gordh
Dept. Surgical Science
Uppsala University

Betygsnämnd:

Doc. Petra Lindfors
Dept Psychology
Stockholms University

Doc. Carl Molander
KIDS
Karolinska Institute

Doc Märta Segerdahl
Dept Fysiol. & Pharmacol
Karolinska Institute

ABSTRACT

Dysfunctions of the autonomic nervous system and of endogenous pain modulation have been reported in fibromyalgia (FM) patients. The dysregulation of the autonomic nervous system, i.e., increased sympathetic activity at baseline and hyporeactivity during exercise and stress, could contribute to muscle ischemia as well as to the exercise intolerance that is typically seen in FM patients.

Isometric contractions are potent stimuli to provoke muscle ischemia, increased muscle pain, heart rate (HR) and blood pressure (BP). In our first two studies we used isometric contractions to investigate the interaction between cardiovascular regulation and pain perception and to assess activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis (HPA-axis) in FM patients. Glia cell activation has been suggested as a possible pathophysiological mechanism in FM and can be linked to dysfunction of autonomic nervous system. Increased levels of pro-inflammatory cytokines have been reported in the blood of FM patients, but cytokines have, to our knowledge, never been studied in the cerebrospinal fluid (CSF) in FM. In study three and four, we investigated pro-inflammatory cytokines in the CSF of patients with FM, rheumatoid arthritis (RA) and controls.

In study 1 we assessed the interactions between cardiovascular regulation and pain perception during static muscle contractions in FM patients and healthy controls. We found that systolic and diastolic BP increased during contraction and decreased following contraction in both groups alike. A significant increase in HR was seen during contraction in FM patients, but not in healthy controls. The rated exertion/fatigue and pain intensity increased more during contraction and remained elevated longer following contraction in the patient group. Pressure pain thresholds (PPTs) were lower in patients compared to controls at all times. No group differences in PPT changes over time were found. In conclusion, no indication of an attenuated cardiovascular response to exercise was found in our FM patients. The more pronounced HR increase in patients during contraction was most likely due to de-conditioning. No exercise related change in PPTs was seen in either group, most likely due to insufficient exercise intensity, but the pain induced by contraction was more pronounced in FM patients.

In study 2 we investigated activation of the sympathetic nervous system and the HPA-axis during static contractions in FM patients and healthy controls. BP and HR increased during contraction and decreased following contraction in both groups alike. Compared to baseline, plasma catecholamines increased during contraction in both groups alike but FM patients had lower levels of plasma adrenaline and a non-significant tendency to lower plasma noradrenaline at all times. No baseline group differences in adrenocorticotropic hormone (ACTH) were found. ACTH increased at exhaustion in controls, but not in FM patients and FM patients had lower ACTH at exhaustion compared to controls. High sensitivity C-reactive protein (CRP) was elevated in FM patients compared to controls. In conclusion, FM patients exhibited a hypoactive sympatho-adrenal system as well as a hypo-reactive HPA-axis during static exercise.

In study 3 we assessed pro-inflammatory cytokines in the CSF and serum in FM patients and headache controls. We reported elevated CSF and serum concentrations of interleukin-8 (IL-8), but not IL-1b, in FM patients. Our conclusion was that the cytokine profile was in accordance with FM symptoms being mediated by abnormal activity in the sympathetic nervous system rather than dependent on prostaglandin associated mechanisms. The results support the hypothesis of glia cell activation in FM.

In study 4 CSF and serum concentrations of pro- and anti-inflammatory cytokines in our FM cohort were compared to patients with an inflammatory rheumatic disease, i.e., rheumatoid arthritis (RA). We found different CSF cytokine profiles with higher concentrations of the pro-inflammatory IL-1b and lower concentrations of the anti-inflammatory IL-1Ra, IL-4 and IL-10 in the CSF of RA patients, compared to FM. FM patients had higher CSF and serum IL-8 concentrations than RA patients. Our results indicate different profiles of central cytokine release, i.e., IL-1b in patients with inflammatory, prostaglandin associated pain (RA) and IL-8 in patients with dysfunctional, possibly sympathetically mediated pain (FM).

Keywords: fibromyalgia, blood pressure, heart rate, pain ratings, exercise, catecholamines, hypothalamo-pituitary-adrenal axis, sympathetic nervous system, autonomic nervous system; glia cells, central inflammation, cytokines, chemokines, lumbar puncture.

ISBN 978-91-7457-669-6