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Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: An experimental study

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Abstract

Deficient endogenous pain inhibition, e.g. Diffuse noxious inhibitory controls (DNIC), or hormonal abnormalities like hypocortisolism, could be responsible for chronic widespread pain in Chronic Fatigue Syndrome (CFS). Thirty-one CFS-patients with chronic pain and 31 healthy controls were subjected to spatial summation of thermal noxious stimuli by gradual immersion (ascending or descending) of the arm in warm water (46 °C). They rated pain intensity every 15 s. Every immersion took 2 min, alternated with 5 min rest. Before and after immersion, salivary cortisol was assessed. Overall pain ratings were higher in CFS-patients, but the evolution was not different between patients and controls, during both ascending and descending immersion. Pain intensity and immersed surface were only correlated during the descending session in both patients ($r = .334$) and controls ($r = .346$). When comparing the first and the last 15 s of every emersion, it was found that pain inhibition starts slower for CFS-patients in comparison to healthy subjects. Both pre- or post-values and cortisol response did not differ between controls and patients. The drop in cortisol was significantly correlated to pain intensity in CFS (r between .357 and .402). In addition to the hyperalgesia in CFS, DNIC react slower to spatial summation of thermal noxious stimuli. We found no evidence for hypocortisolism in CFS, and the cortisol response to nociception was not different in CFS compared to healthy subjects. In conclusion, delayed pain inhibition may play a role in chronic widespread pain in CFS but further research is required.

Keywords: Cortisol; HPA-axis; Spatial summation; Diffuse noxious inhibitory controls (DNIC); Pain; Chronic fatigue syndrome (CFS)

1. Introduction

In Chronic fatigue syndrome (CFS) major concerns seem fatigue and increased fatigability. Research regarding chronic pain in CFS is lacking, although the majority of CFS-patients also suffers chronic widespread pain [20]. Considering the widespread localization of the pain and the absence of tissue damage, it has been suggested that central neural mechanisms may be responsible [19]. Central sensitization may be elicited by wind-up of *N*-methyl-D-aspartate receptors after prolonged firing of C-fiber nociceptors [3]. Besides, disruption of elements of descending pain inhibitory pathways can result in the equivalent of central sensitization [37]. To our knowledge, only the lack of analgesia following exercise is reported to document deregulated anti-nociceptive mechanisms in CFS [33].

In Fibromyalgia (FM), investigations concerning pain processing are abundant. Deregulation of endogenous pain inhibition has been documented by the default of analgesic effects due to exercise [13,26,30] and in studies evaluating the efficacy of "Diffuse noxious

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inhibitory controls" (DNIC). DNIC rely on painful conditioning stimulation of one part of the body to inhibit pain in another part [4], to remove the "noise" and to focus on relevant stimuli. In contrast to healthy controls, applying conditioning noxious stimuli on one body part does not result in increased pain thresholds elsewhere in FM-patients [14,15]. DNIC also interfere with spatial summation of pain (SSP) [18]. SSP depends on the number of central neurons recruited [24] and thus the stimulated area. As the stimulated area increases, inhibitory interactions may take place between nociceptive afferent inputs within this area. For example, progressive immersion of the hand and arm in hot water might cause nociceptive input from the hand (=conditioning stimulus) to inhibit nociceptive input from the arm, as suggested by Marchand and Arsenault [18]. Deregulated DNIC could be documented in FM-patients by evaluating the SSP [11].

Besides neural mechanisms, hormonal abnormalities could cause altered pain processing. Cortisol is released in answer to pain and has the capacity to suppress pain [21]. Given the evidence for hypofunction of the hypothalamic-pituitary-adrenal axis in a proportion of CFS-patients [5,29], the relation between pain and cortisol in CFS-patients may be an interesting topic to consider.

This study aimed at evaluating endogenous pain inhibition, more specific DNIC and the cortisol response, by spatially summating thermal nociceptive stimuli in CFS-patients with chronic widespread pain.

We anticipated a lack of inhibitory efferent recruitment to counter nociceptive input in CFS-patients, leading to spatial summation and equal pain sensation during both increasing and decreasing immersion of the arm in hot water. In healthy controls, appropriate pain inhibition would compensate the increasing nociceptive input during increasing immersion of the arm. Complete recruitment of inhibitory efferents at the beginning of the descending immersion would lead to overcompensation of inhibition as the immersed surfaces decrease, resulting in lower pain intensities compared to the ascending immersion. In CFS-patients, this overcompensation would not occur due to the lack of complete inhibition recruitment, resulting in equal pain sensations. Furthermore, we assumed lower baseline cortisol levels and a blunted response to nociceptive stimuli in CFS-patients.

2. Methods

2.1. Subjects

Patients were selected by randomly selecting their medical files from the files available at our university-based chronic fatigue clinic. All patients fulfilled the 1994 Centre for Disease Control and Prevention (CDCP) criteria for CFS [10]. Therefore, all subjects underwent an extensive medical evaluation by the same physician, specialized in internal medicine, prior to study participation (see below). In addition, patients suffered from chronic widespread pain as described in the 1990 criteria of the American College of Rheumatology, namely pain located axially on the left and the right side of the body and above and under the waist, lasting for more than 3 months [34]. Allodynia was not evaluated.

Healthy control subjects were recruited among the staff and students of the Physiotherapy Department of the University College Antwerp, and among friends and family of the researchers. They reported to be healthy and pain-free. Healthy controls were age- and gender-matched to the CFS-patients.

Only Dutch speaking participants aged between 18 and 65 qualified for this study. All pain-related treatment, anti-inflammatory drugs, antidepressants with analgesic effects and steroids were withdrawn 48 h before testing. This duration was chosen based on ethical considerations and based on the fact that analgesic effects are mostly limited in time. Furthermore subjects were asked not to undertake physical exertion, and to refrain from consuming caffeine, alcohol or nicotine on the day of the experiment.

Subjects were excluded from the study if they were pregnant, had cardiovascular or neurological diseases or if they had diabetes.

Thirty-one CFS-patients and 31 healthy controls were included.

2.2. Diagnosis of CFS

To fulfill the CDCP criteria for CFS, a clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset should result in a substantial reduction in the previous levels of occupational, educational, social, or personal activities [10]. Furthermore, at least four of the following symptoms must have persisted or recurred during 6 or more consecutive months and must not have predated the fatigue: impairment in short-term memory or concentration, tender cervical or axillary lymph nodes, muscle pain, multijoint pain, headache, unrefreshing sleep, and post-exertional malaise >24 h [10]. Any active medical condition, which may explain the presence of chronic fatigue, prohibits the diagnosis of CFS. Hence, all subjects underwent an extensive medical evaluation, consisting of a standard physical examination, medical history, exercise capacity test and routine laboratory tests. The laboratory tests included a complete blood cell count, determination of the erythrocyte sedimentation rate, serum electrolyte panel, measures of renal, hepatic and thyroid function, as well as rheumatic and viral screens. If the patients' medical history did not exclude a psychiatric problem at the time of disease onset, then a structured psychiatric interview was performed. In a number of cases further neurological, gynecological, endocrine, cardiac and/or gastrointestinal evaluations were performed. The medical records were also reviewed to determine if patients suffered from organic or psychiatric illness that could explain their symptoms. If any of the laboratory/additional analyses revealed any active medical condition, which may explain the presence of the patient's symptoms, then the subject was excluded from the sample.