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Alterations in excitatory and inhibitory brainstem interneuronal circuits in fibromyalgia: Evidence of brainstem dysfunction

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HIGHLIGHTS

- Fibromyalgia syndrome (FMS) patients present with altered stimulus perception and processing and report pain following non-noxious stimuli.
- Pedunculopontine nucleus – assessed by prepulse inhibition of blink reflex – plays crucial role in sensory gating mechanisms.
- Reduced prepulse inhibition concurs with less filtering of afferent input at brainstem level, and may thus contribute to abnormal sensory processing in FMS.

ABSTRACT

Objective: Patients with fibromyalgia syndrome (FMS) perceive stimuli differently and show altered cortical sensory representation maps following peripheral stimulation. Altered sensory gating may play a causal role.
Methods: Blink reflex, blink reflex excitability recovery, and prepulse inhibition of the blink reflex – representing brainstem excitability – were assessed in 10 female patients with FMS and 26 female healthy controls.
Results: Unconditioned blink reflex characteristics (R1 latency and amplitude, R2 and R2c latency and area-under-the-curve) did not differ significantly between patients and controls. Blink reflex excitability recovery was enhanced in patients versus controls at all intervals tested. Prepulses significantly suppressed R2 area and increased R2 latency in patients and controls. However, R2 area suppression was significantly less in patients than in controls (patients: to 80.0 ± 28.9%, controls: to 47.8 ± 21.7%). The general pattern of corresponding changes in R2c was similar.
Conclusions: Blink reflex is normal, whereas blink reflex excitability recovery is enhanced and blink reflex prepulse inhibition is reduced in patients with FMS, suggesting functional changes at the brainstem level in FMS.
Significance: Reduced blink reflex prepulse inhibition concurs with altered sensory gating in patients with FMS.

1. Introduction

Fibromyalgia syndrome (FMS) is one of the most common causes of chronic widespread pain. Patients typically suffer from hyperalgesia and allodynia (Clauw, 2009) and often from a wide range of symptoms including fatigue, sleep disturbance, cognitive dysfunction, mood disturbance, irritable bowel disease, restless legs syndrome, and headache. The incidence of FMS peaks between 20 and 55 years, but it may occur at any age. Prevalence increases with age, and females outnumber males between 3:1 and 7:1 (Carville et al., 2009).

In 1990, the American College of Rheumatology (ACR) published classification criteria in order to identify patients with FMS and to facilitate research (Wolfe et al., 1990). Although primarily aimed at research, these classification criteria are also widely used to diagnose FMS in daily clinical practice. Several shortcomings led to a recently published revision of these criteria (Wolfe et al., 2010).

Pathophysiology and pathogenesis of FMS are still unknown, but abnormal pain processing seems to play a fundamental role.

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Abnormal perception of pain is a key feature of FMS (Ceko et al., 2012). Pain resulting from innocuous mechanical stimuli such as brushing the skin corresponds to allodynia and is likely to be an important pathophysiological component of fibromyalgia symptomatology (Fallon et al., 2013). Pressure stimuli evoke larger magnetoencephalographic responses in FMS patients compared to healthy controls in somatosensory, temporal and parietal areas at short latencies, and in prefrontal areas at both short and long latencies, even when adjusted to produce similar subjective pain levels (Maestu et al., 2013). Both hyperalgesia and allodynia may result from peripheral or central sensitisation, to which several factors may contribute (Carville et al., 2009). Neuroimaging studies provide evidence of augmented sensitivity to heat and pressure stimuli, as well as diminished activation of pain inhibitory systems (Gracely and Ambrose, 2011).

FMS patients utilize more extensive brain resources than do age-matched healthy subjects in order to achieve comparable performance on cognitive tasks (Williams and Gracely, 2006). Conscious awareness of afferent sensory information is regulated by thalamic relay centers. Additionally, the brainstem is involved in filtering afferent information flow to the brain, in particular the pedunculopontine nucleus (PPN). The PPN is involved in prepulse inhibition (PPI), which seems to be the fundamental neurophysiological mechanism underlying sensory gating at the brainstem level (Swerdlow and Geyer, 1993; Valls-Solé et al., 1999; Kumari et al., 2003; Frauscher et al., 2012). The presumed underlying circuit that mediates PPI in humans has recently been suggested by Valls-Solé et al. (2008).

We hypothesized that PPI is deficient in patients with FMS. Less PPI may concur with "less rigorously filtered" sensory information conveyed to the brain, thereby contributing to altered sensory processing. We therefore compared PPI of the blink reflex and blink reflex excitability recovery in FMS patients and healthy control subjects in order to obtain an estimate of brainstem reflex excitability.

2. Subjects and methods

2.1. Selection of patients and control subjects

Ten patients with FMS according to ACR criteria (Wolfe et al., 1990) were included and compared to 26 healthy control subjects, who were recruited from hospital staff and their relatives. All patients were females and suffered from widespread pain defined as axial pain and right- and left-sided pain, including arms and legs, for more than 1 year. Furthermore, they all had abnormal tenderness in at least 11 of 18 anatomically defined locations (i.e., tender points) according to the 1990 ACR criteria of fibromyalgia (Wolfe et al., 1990). Patients also complained of several other disorders, all common in FMS: eight patients suffered from fatigue, six complained of sleeping disorders (i.e., non-restorative sleep), six of mood disturbance, four of tension headache, three of dizziness and one of unspecific abdominal sensations. All patients presented with pain ratings mostly above 5 on a 10-cm visual analog scale (VAS, 0 = no pain; 10 = maximum pain). As common in FMS, VAS pain ratings varied from day to day but patients were never pain-free during the observation period. Finally, patients presented with brisk tendon jerks, but no pyramidal signs. One patient had a history of neck pain due to disc protrusion, but was free of symptoms at time of study and was taking no medication. Magnetic resonance imaging revealed no intramedullary signal alteration or nerve root contact. No other relevant comorbidities were noted. Patients were allowed to continue their medication, as more pain would likely have resulted in untoward tension, precluding valid neurophysiological testing (Table 1). "Healthy" was defined as self-reported well-being, and no history of psychiatric or neurological disease. Control subjects denied use of any centrally active medication or drug abuse at time of investigation and the preceding 48 h. All participants were asked to refrain from smoking and drinking caffeinated beverages within 4 h of the study. Exclusion criteria were any definite or suspected diagnosis of co-morbid psychiatric disease. No participant had her blink reflex tested before. This study was approved by the local Institutional Review Board in compliance with the Declaration of Helsinki. All participants granted informed consent.

Table 1
Patient demographics.

Number	Age (years)	Disease duration (years)	Medication	Dose/day (mg)
1	40	>10	Pregabalin	300
			Fluoxetin	40
			Tramadol	300
			Trazodon	150
2	67	>10	Citalopram	20
3	54	>5	Duloxetin	60
			Trazodon	100
4	40	>10	None	
5	53	>10	Escitalopram	10
			Tetrazepam	50
			Zolpidem	10
6	54	>2	None	
7	33	>10	Gabapentin	900
8	50	>10	Hydropmorphon	4
			Orphenadrin	105
			Paracetamol	1350
			Duloxetin	60
9	51	>2	Duloxetin	90
			Amitryptilin	75
10	40	>2	Duloxetin	60

2.2. Neurophysiological investigation

All neurophysiological studies were carried out by the same investigator (MK) with participants lying in supine position at room temperature, using routine electrodiagnostic equipment (Nicolet Viking IV, Madison, WI, USA).

2.3. Blink reflex

Single sweeps of non-rectified electromyographic activity of the orbicularis oculi muscles were recorded bilaterally with 10-mm-diameter surface gold electrodes attached to the skin, the active electrode in the middle portion of the muscle below each eye, and the reference electrode lateral to the outer canthus. The electromyographic signal was amplified (1000×) and band-pass filtered (30–3000 Hz). Blink reflexes were evoked by electrical stimuli (0.5 ms rectangular pulses) delivered to the right supraorbital nerve with surface electrodes, cathode over the supraorbital notch and anode 3 cm above along the course of the nerve on the forehead. We used 10 times sensory threshold intensity to elicit the blink reflex in eight trials with at least 10 s interval between two consecutive trials. Sensory threshold was defined as the minimum intensity that was perceived in at least four out of eight stimulations.

2.4. Excitability recovery curve of the blink reflex

For establishing excitability recovery curves of the blink reflex, paired pulses were delivered to the supraorbital nerve at the following interstimulus intervals: 160, 300, and 500 ms (Kimura and Harada, 1976; Kofler et al., 2013). Six traces of rectified EMG