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Facilitated temporal processing of pain and defective supraspinal control of pain in cluster headache

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ABSTRACT

In cluster headache (CH), pathogenesis has been emphasized the role of the posterior hypothalamus. It is part of a supraspinal network involved in the descending control of pain, including the diffuse noxious inhibitory control (DNIC), which in turn modulates the pain processing. We hypothesized that CH during the active phase facilitated temporal pain processing supported by abnormal functioning of the DNIC. We studied the functional activity of the DNIC by evaluating the effect of the cold pressor test (CPT) on the temporal summation threshold (TST) of the nociceptive withdrawal reflex. Ten subjects with episodic CH (2 women, 8 men) and 10 healthy subjects were recruited. Each subject underwent neurophysiological evaluation (nociceptive withdrawal reflex TST and related painful sensation) at baseline, then before (control session), during (pain session), and 5 min after (aftereffect) the CPT (immersing hand in a 4 °C water bath for 4–5 min). Patients had been studied during both the active and remission phases. During the active phase, CH revealed a significant facilitation in temporal processing of pain stimuli (reduction of TST), which reverted during the remission phase. The CPT activating the DNIC did not produce any significant inhibitory effect of pain responses in CH during the active phase, whereas it induced a clear inhibition during the remission phase. We hypothesized that in CH, a dysfunction of the supraspinal control of pain related to the clinical activity of the disease, possibly supported by an abnormal hypothalamic function, leads to a facilitation in pain processing and a predisposition to pain attacks.

1. Introduction

Cluster headache (CH) is a rare primary headache disorder characterized by strictly unilateral headache attacks accompanied by ipsilateral autonomic symptoms, resulting from activation of the trigeminal nerve and craniofacial parasympathetic nerve fibers [11]. The pathogenesis of CH is not completely clear. However, in view of the striking circadian rhythm of the pain attacks, the relapse–remission course, the seasonal recurrence of the cluster periods, and the neuroendocrinological and structural neuroimaging evidence, the posterior hypothalamus likely plays a major pathogenetic role [20,21,37]. Nevertheless, it remains unknown whether the hypothalamus's playing a role in triggering, terminating, or activating pain represents an epiphenomenon during the pain phase [33]. Studies have revealed that the chronic hypothalamic direct stimulation reduces CH pain recurrence [3,16,34]. Interestingly, the late onset of the clinical effect after the stimulation, coupled with the inefficacy of acute treatment [15], suggests that the hypothalamus could play a role as a modulating structure rather than in triggering pain.

The hypothalamus is part of an integrated neuronal network including structures such as the somatosensory cortex, thalamus, periaqueductal gray (PAG), subnucleus reticularis dorsalis (SRD), and rostroventral medulla (RVM), which diffusely project throughout the central nervous system to modulate pain processing in a top-down manner [4,10,14,18]. In this sense, in humans, consistent evidence supports an important pain-modulating role for the diffuse noxious inhibitory control (DNIC), a system operating via a spinal-bulbo-spinal adrenergic loop mediated through antinociceptive structures including PAG, SRD, and RVM that exerts modulatory influences at trigeminal and spinal level by direct

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descending inhibitory projections on wide dynamic range (WDR) neurons mediating wind-up phenomenon in animals and temporal summation (TS) of pain in humans [10,13,22,38].

Wind-up and TS of pain represent a form of short-term neuronal plasticity that subserves integration of sensory stimuli in the central nervous system through a temporary change in sensory neuron excitability—a shifting of the sensory information from tactile to nociceptive—before transmitting the nociceptive inputs to the higher centers of the brain that in turn regulate pain processing by descending brain stem pathways, such as DNIC [7,22]. One of the most typical abnormalities resulting from pain processing dysfunction is represented by the activity-dependent changes in the excitability of central neurons resulting in an abnormal TS of pain stimuli [8]. Interestingly, from a clinical point of view, a rapid onset of cutaneous allodynia in the trigeminal and extracephalic areas both during and outside attacks has been described in almost 50% of CH subjects [2,9,19,27]. This clinical evidence may reflect a change in the excitability of pain pathways and could be supported by a dysfunctional supraspinal pain control such as DNIC.

The functional activity of the DNIC and the TS of pain can be tested in men through objective methods such as the cold pressor test (CPT) and the temporal summation threshold (TST) of the nociceptive withdrawal reflex (NWR) [23,25,35].

We hypothesized that during the active phase of the disease, CH patients would display a defective functioning of the supraspinal pain control, thus impairing the temporal processing of the nociceptive inputs and predisposing them to the pain attack. To test our hypothesis, we studied the functional activity of the DNIC by evaluating the effect of the CPT on the TST of the NWR in CH patients during the active and remission phases of the disease and comparing them with healthy subjects.

2. Materials and methods

The study was approved by the local ethics committee (No. 04/2010) and was carried out following the guidelines for proper human research conduct in accordance with the Helsinki Declaration of 1975, revised 2000. All participants provided written informed consent.

2.1. Study population

2.1.1. Patients

Ten patients (2 female, 8 male) diagnosed as having episodic CH according to the diagnostic criteria set out in the second edition of the International Classification of Headache Disorders [11] were enrolled at the outpatient service of the Headache Clinic of the Mediterranean Neurological Institute "Neuromed," Pozzilli, Isernia, Italy.

Patients with CH experienced strictly unilateral pain (6 right side, 4 left side). Other primary or secondary headaches were excluded by clinical and/or instrumental evaluation, as appropriate. Exclusion criteria included any serious systemic or neurological disease or psychiatric disorder, ongoing use of prophylactic medication for CH (in the previous 2 months), current use of antidepressive and antiepileptic medications or analgesics; clinical or instrumental evidence of any central or peripheral disease potentially causing sensory impairment; fibromyalgia, neuropathic pain, complex regional pain syndrome, and other pain conditions, according to current guidelines. CH patients with family history (first-degree relatives) of migraine were excluded.

Participants' demographic and clinical characteristics are reported in Table 1.

2.1.2. Healthy subjects

Ten age- and sex-matched (2 female, 8 male), healthy individuals without neurological disorders or a clinical history (including family history) of neurological disorders were recruited as the control group (Table 1).

2.2. NWR measurements

2.2.1. Nociceptive withdrawal reflex

The NWR from the lower limb was investigated according to a validated method [30]. In particular, women and controls were matched for cycle phases (follicular phase) to minimize the pain modulation across the menstrual cycle [30], and all the subjects were tested between 9 am and 11 am to minimize the effect of diurnal variation [30]. Before formal measurements began, the subjects underwent training to familiarize them with the pain threshold assessment procedure. The subjects were seated comfortably in a quiet room at a constant temperature (23 ± 2 °C). Their lower limbs were positioned to ensure complete muscle relaxation (knee flexed at 130° and ankle at 90°).

The sural nerve was stimulated percutaneously via a pair of standard surface electrodes (Ag/AgCl) applied to degreased skin behind the right lateral malleolus. The transcutaneous electrical stimulus consisted of a constant current pulse train of 5 individual 1 ms pulses delivered at 200 Hz (equal to an interstimulus interval of 4 ms), randomly applied every 25–40 s. Electromyographic reflex responses were recorded from the capitis brevis of the biceps femoris via surface electrodes (Ag/AgCl). The filter band pass setting was between 3 Hz and 3 kHz.

The analysis time was 300 ms, with the sensitivity set at 100 mV. Each response was full-wave rectified and integrated in the 80–130 ms poststimulus interval [30] (CED Powerlab interface 1401, Cambridge Electronic Design, UK; electronic amplifier BM623, Biomedica Mangoni, Italy; electric simulator DS7A, Digitimer, UK). The staircase method was used to evaluate the NWR threshold (Th), defined as the stimulation intensity generating stable reflex responses with an amplitude exceeding 20 μV for more than 10 ms in the time interval 80–130 ms over 5 stimuli. The stimulation intensity was fixed at 1.2 × Th; 5 reflex responses were recorded, and the mean NWR area under the curve (Area) was computed by a computerized method.

The subjects rated the psychophysical pain sensation for each stimulus on an 11-point numerical rating scale (NRS), graded from 0 (no pain) to 10 (unbearable pain).

The first recording of each session was discarded in an attempt to reduce the influence of the startle reaction.

2.2.2. TS of the NWR

The sural nerve was stimulated with a constant current pulse train of 5 individual 1-ms pulses delivered at 200 Hz repeated 5 times at a frequency of 2 Hz, as previously described [1].

The current intensity was increased (in 1-mA steps) from 2 mA until detection of TS. A TST of the NWR was considered when a clear facilitation of the reflex response size (greater than 20 μV for 10 ms or more) in the fourth and fifth trace, compared to the first one, was detectable during the course of the train of 5 individual pulses in the time interval 80–130 ms and was accepted when 3 consecutive recordings gave the same threshold.

The subjects rated the psychophysical pain sensation for the first and fifth stimulus at TST on an 11-point NRS, graded from 0 (no pain) to 10 (unbearable pain).

2.3. Heterotopic noxious conditioning stimulation

In order to study the pain modulating system subserving DNIC, we investigated the effects of experimental heterotopic noxious conditioning stimulation, in the form of the CPT, on the TST and Area as well as on the related psychophysical measurements