Pain 118 (2005) 137–144

PAIN

www.elsevier.com/locate/pain

Multilevel somatosensory system disinhibition in children with migraine

Massimiliano Valeriani*, Steno Rinalduzzi, Federico Vigevano

Headache Center, Divisione di Neurologia, Ospedale Pediatrico Bambino Gesù, IRCCS, Piazza Sant'Onofrio 4, 00165 Rome, Italy

Received 30 March 2005; received in revised form 19 July 2005; accepted 1 August 2005

Abstract

Although migraine is characterised by an abnormal cortical excitability level, whether the central nervous system is hyper- or hypo-excitable in migraine still remains an unsolved problem. The aim of our study was to compare the somatosensory evoked potential (SEP) recovery cycle, a marker of the somatosensory system's excitability, in a group of 15 children suffering from migraine without aura (MO) (mean age 11.7 ± 1.6 years, five males, 10 females) and 10 control age-matched subjects (CS) (mean age 10.9 ± 2.1 years, six males, four females). We calculated the SEP's latency and amplitude modifications after paired electrical stimuli at 5, 20 and 40 ms interstimulus intervals (ISIs), comparing it with a single stimulus condition assumed as the baseline. In MO patients, the amplitudes of the cervical N13 and of the cortical N20, P24 and N30 responses at 20 and 40 ms ISIs showed a higher recovery than in CS (two-way ANOVA, $P < 0.05$). Since, the SEP recovery cycle depends on the inhibitory interneuron function, our findings suggest that a somatosensory system disinhibition takes place in migraine. This is a generalized phenomenon, not limited to the cerebral cortex, but concerning also the cervical grey matter. The SEP recovery cycle reflects the intracellular concentration of Na^+, therefore, the shortened recovery cycle in our MO patients suggests a high level of intracellular Na^+ and a consequent depolarized resting membrane potential, possibly due to an impaired Na^+–K^+ ATPase function in migraine.

Keywords: Migraine; Somatosensory evoked potentials; Pain; Children; Human brain

1. Introduction

In migraine, the reduced habituation to the afferent inputs during the interictal phase is one of the most characteristic neurophysiological features (see Ambrosini et al., 2003; Schoenen et al., 2003 for reviews). Due to habituation, the evoked potential (EP) amplitude, which is a quantitative index of the neuronal population activated by certain sensory inputs, tends to decrease during repetitive sensory stimulation, due to a progressive reduction of the neuronal response. In migraine, experimental studies aiming at the investigation of the EP modification after repetitive stimulation showed a lack of habituation in both children and adults (Afra et al., 1998, 2000; Evers et al., 1997, 1998; Grosser et al., 2000; Maertens de Noordhout et al., 1986; Ozkul and Uckardes, 2002; Sand and Vingen, 2000; Sartory et al., 1997; Valeriani et al., 2003). This phenomenon was believed to be caused either by an increased or by a reduced cortical excitability. The threshold for phosphene induction by transcranial magnetic stimulation of the occipital cortex, lower in patients with migraine than in healthy subjects, suggests that in the former group the brain is hyperexcitable (Aurora et al., 1998). However, Bohotin et al. (2002) recently demonstrated the recovery of a normal habituation pattern of the P100 visual evoked potential (VEP) in migraineurs after high frequency (10 Hz) repetitive transcranial magnetic stimulation (rTMS) of the occipital cortex. On the contrary, control subjects submitted to low frequency (1 Hz) rTMS of the occipital cortex showed no P100 amplitude habituation. Since, the rTMS at 10 Hz and at 1 Hz, respectively, increases and reduces the cortical excitability, the authors suggested that migraineurs show a normal habituation when their cortical excitability is raised up to the level of healthy subjects, who, on the contrary, lose the VEP habituation if their occipital cortex is inhibited. According to these results, in the interictal phase of migraine there is a cortical hypoexcitability, and the lack

* Corresponding author. Tel.: +39 0668592289; fax: +39 0668592463.
E-mail address: m.valeriani@tiscali.it (M. Valeriani).

0304-3959/$20.00
doi:10.1016/j.pain.2005.08.026

of habituation can be explained by the 'ceiling effect model' (Knott and Irwin, 1973; Schoenen, 1996). In this model, the habituation depends on the pre-activation level of the cerebral cortex, which is very low in migraine, and prevents any further excitability reduction.

A marker of the SI area excitability is represented by the SEP recovery cycle. It is known that when SEPs are obtained by two paired electrical shocks at different interstimulus intervals (ISIs), the SEP amplitude evoked by the later stimulus is smaller than the one recorded from a single stimulus. The longer is the ISI, the higher is the amplitude of the SEPs recorded after the second stimulus, until a complete amplitude recovery is observed (Angel et al., 1985; Emori et al., 1991; Meyer-Hardting et al., 1983; Romani et al., 1995; Shagass and Schwartz, 1964). The aim of our study was to investigate the SEP recovery cycle in patients with migraine. According to our hypothesis, if the excitability of the SI area is increased in migraine, the recovery of the SEP amplitude should take a shorter time in migraineurs than in healthy subjects.

2. Materials and methods

2.1. Subjects

Twenty-five subjects, whose parents gave an informed consent, took part in this study. Fifteen patients had migraine without aura (MO) (mean age 11.7 ± 1.6 years, five males, 10 females) and 10 healthy children were the control subjects (CS) (mean age 10.9 ± 2.1 years, six males, four females). MO patients were diagnosed according to the criteria of the International Headache Society (2004). All of them had had the first migraine attack at least 1 year before being included in our study. We made sure that they did not suffer from any other neurological or internal disease. The SEP recordings were performed no sooner than 72 h after the last headache attack. Moreover, in no patient a headache attack followed the SEP recording in the next 72 h. No MO patient took any drug during the 72 h before the SEP recording was performed. In selecting the CS, children whose first- or second-degree relatives suffered from migraine were excluded from the study.

2.2. SEP recording

For SEP recording, subjects lay in a couch in a quiet and semidarkened room. Right and left median nerves were stimulated at the wrist by surface electrodes at an intensity just able to produce a motor twitch (stimulus duration: 0.2 ms, stimulus rate: 2 Hz). SEPs were recorded from four electrodes (impedence < 5 kΩ) placed: (1) at Erb's point ipsilateral to the stimulation (Erb_i), referred to an electrode at the contralateral Erb's point (Erb_c); (2) over the 6th cervical vertebra (C6), referred to an anterior electrode above the thyroid cartilage (AC); (3) over the parietal area contralateral to the stimulation (P3/P4); (4) over the frontal midline (Fz). The scalp electrodes were referred to an electrode at the earlobe ipsilateral to the stimulated side (Au1/Au2). The ground was at the stimulated arm. The analysis time was 100 ms, with a sampling rate of 20 kHz. The amplifier band-pass was 10–2000 Hz (12 dB roll-off). One average of 1000 trials was obtained in each of the conditions (i.e. single stimulus or double stimulus) and printed out.

2.3. SEP recovery cycle

For investigating the SEP recovery cycle, we used a paired stimulation technique, similar to that of previous studies (Emori et al., 1991; Meyer-Hardting et al., 1983). SEP recording to a single stimulus was taken as control. Moreover, three further recordings were performed by using two paired stimuli at different ISIs (5, 20, and 40 ms). In the double-stimulus traces, the responses following the second stimulation were obtained by subtracting the control SEP waveforms from the waveforms following each double stimulus.

2.4. SEP analysis

SEPs were identified according to their latency and polarity. The peripheral N9 potential was recorded by the Erb_i electrode, while the spinal N13 response was identified in the C6-AC trace. Both scalp electrodes (P3/P4 and Fz) recorded the lemniscal P14 component, which was measured in the frontal trace where it shows the highest amplitude (Restuccia et al., 1995). The parietal N20 and P24 responses were recognizable in the parietal trace, while the N30 potential was recorded by the frontal lead. SEP amplitude was measured from the previous peak of opposite polarity. SEP latencies and amplitudes following a single stimulus, recorded both on the left and right side of the subject, were compared by using the paired Student's *t*-test and the Wilcoxon test, respectively. In the single stimulus condition, the unpaired Student's *t*-test and the Mann–Withney test were performed to compare SEP latencies and amplitudes respectively among MO patients and CS. Two-way ANOVA was used to compare the recovery cycle of the SEP latencies among MO patients and CS, by considering the group (i.e. patients or CS) and the ISI as sources of variability. In order to reveal possible differences between the SEP amplitude recovery cycle of MO patients and that of the CS, the SEP amplitudes in the double stimulus conditions were normalized as the percentage of the corresponding SEP amplitude obtained after a single stimulus, which was assumed as 100%. The SEP amplitudes to double stimuli at different ISIs were then compared by means of the two-way ANOVA, considering the subject group (patients or CS) and the ISI as variables. Post hoc analysis was performed by means of the Student's *t*-test with Bonferroni's correction for multiple comparisons. Amplitudes of the cortical SEP components (N20, P24 and N30) were compared to the lemniscal P14 amplitude at the ISIs of 20 and 40 ms by using the Spearman's correlation test, in order to make sure that the recovery cycle of the cortical potentials did not depend on the one of the brainstem P14 response. The level for statistical significance was fixed at $P < 0.05$.

3. Results

3.1. SEP amplitude and latency

In the single stimulus condition, the comparison of SEP amplitudes and latencies recorded from the two sides