Short latency trigemino-
sternocleidomastoid response in patients with migraine

Abstract  Objective To investigate the central trigeminal circuits in migraine patients. Materials and methods Short latency responses can be recorded in sternocleidomastoid (SCM) muscles after stimulation of the trigeminal nerve (trigemino-cervical reflex). This brainstem reflex was investigated in 20 healthy subjects, in 20 patients suffering from migraine with aura (MWA) and in 20 patients suffering from migraine without aura (MWOA) during and between the attacks. Results The trigemino-cervical responses were bilaterally abnormal in 17 patients with MWA and 15 patients with MWOA during the headache attacks, in 11 patients with MWA and in 10 patients with MWOA during the interictal period. In the patients with normal trigemino-cervical responses during the pain-free phase the triptan was significantly more effective at relieving headache. Conclusions Our findings further support and emphasise the role of the trigeminal system in the pathogenesis of migraine. The bilateral location of the abnormalities suggests a centrally located dysfunction. Therefore, the trigemino-cervical reflex is sensitive in disclosing a disturbed brainstem activity and may be an index of neuronal activity in the human brainstem; moreover their assessment may help as valuable prognostic tool for predicting the efficacy of triptans therapy.

Keywords  migraine · trigemino-cervical reflex · triptans · sumatriptan

Introduction

Current theories propose that the trigeminal system is intimately involved in the pathogenesis of migraine. One of the key pathophysiological mechanisms underlying the generation of headache pain associated with migraine is proposed to be the activation of this “trigeminovascular system” [17,19]; that is local vasodilatation of intracranial extracerebral blood vessels and the consequent stimulation of surrounding trigeminal sensory nervous pain pathways. Orthodromic conduction along the activated trigeminal fibers transmits nociceptive information to central neurons in the trigeminal and other brainstem sensory nuclei that in turn relay the pain signal to higher cortical structures where headache pain is perceived.

The advent of triptans is considered to be a revolu-
be recorded in neck muscles after stimulation of branches of the trigeminal nerve [8]. The trigemino-cervical reflexes consist of a bilateral positive/negative wave in the average of the unrectified surface EMG, corresponding to a short period of inhibition of voluntary motor unit firing. The clearest responses were seen in the tonically active sternocleidomastoid (SCM) muscle after stimulation of the infraorbital nerve, in accordance with previous studies [9, 11]. The aim of the present study was to further elucidate the pathophysiology of migraine with special reference to central mechanisms (in particular the involvement of the trigeminal brainstem system) and to evaluate the clinical usefulness of this brainstem reflex in predicting the efficacy of the acute treatment with triptans.

**Methods and patients**

We investigated the trigemino-cervical reflex in 54 healthy volunteers, in 20 patients suffering from migraine with aura (MWA) and in 20 patients suffering from migraine without aura (MWOA).

**Neurophysiological procedures**

Surface EMG activity was recorded bilaterally from symmetrical sites over the upper half of the active SCM muscle ~ 8 cm above a reference electrode on the clavicle, while subjects held the head slightly raised when lying supine. The EMG was amplified, bandpass filtered (30 to 3000 Hz), and averaged (usually 512 trials) from 20 ms before the stimulus to 80 ms afterward. Electrical stimuli (100 µs duration) were applied to the infraorbital nerve via bipolar surface electrodes fixed near the point of exit from the skull. The intensity was adjusted to be three times perceptual threshold, which most subjects regarded as strong but not painful. The repetition rate was usually 3 Hz. Amplitudes were measured peak to peak in the unrectified average. The reason for this procedure is indicated in detail elsewhere [8]. Because the size of EMG responses is linearly related to the degree of background muscle contraction, we expressed the size of the potentials as a ratio to the mean rectified surface EMG activity preceding the stimulus [8]; flexion of the head against gravity gave a mean EMG activity ranging from 50 to 140 µV, and the normal amplitude limits were determined for this level of activity. The size of the responses varied considerably from subject to subject. To transform the distribution of the data into a more Gaussian form, we took the square root of the amplitude values before determining the normal limits. Normal limits were defined as mean ± 2.5 SD of the values in control subjects; for transformed data, the limit of normal was converted back to an untransformed ratio.

**Patients**

Patients included in the study were outpatients who had at least a 6-month history of moderate or severe migraine with aura (20 subjects, 12 women and 8 men, mean age 40, range 22–56) and without aura (20 subjects, 13 women and 7 men, mean age 38, range 24–58) according to the criteria of the International Headache Society [16]; these patients experienced 2 to 4 attacks of unilateral pain per month, lasting between 8 to 48 hours.

All subjects underwent a complete neurological examination to confirm the diagnosis and were asymptomatic between attacks. There was no history or clinical evidence of chronic daily headache, cervical spine disorders, headache associated with vascular and nonvascular disorders, overuse symptomatic medication, another neurological illness. Brain magnetic resonance imaging (MRI) or enhanced computed tomography (CT), performed in all patients, did not show any abnormalities. Only women who did not have coexisting or previous premenstrual/menstrual migraine were included in our study, the stage of each subject’s menstrual cycle was calculated on the day of the assessment.

The investigators were blinded as to the status of the subject (patient/control). No patient received any prophylactic treatment; only medication with triptans (11 of them were taking sumatriptan, 2 rizatriptan and one zolmitriptan) and occasionally non-steroidal anti-inflammatory drugs (NSAID) was used; neither group last used any non-steroidal analgesics at least 5 days before the study.

All patients received for the acute treatment of the migraine attack oral sumatriptan 100 mg. The electrophysiological studies were carried out during the headache phase within the first 2 hours (mean time 40 min.) from the beginning of a spontaneous migraine attack and during the interictal period, at least 2 days between migraines.

Electrophysiological findings were correlated with the neurological disability before, 2 hours and 4 hours after the patients had taken oral sumatriptan; subjective headache severity was rated using a four-point anchored Verbal Rating Scale (VRS-4: headache severity 0 = no headache, 1 = mild headache, 2 = moderate headache and 3 = severe headache).

Analysis of variance (ANOVA) was used to compare latencies and amplitudes of the three groups, with Bonferroni corrections for multiple comparisons. Results are considered significant if p < 0.05. The relation between different variables was evaluated by means of the Spearman’s r correlation coefficient.

The age-matched control group consisted in 54 healthy subjects (24 women and 30 men, mean age 40.2 years, range 20–67); they had no history of neurological illness, headache or facial pain and a normal neurological examination.

The study was approved by the institutional ethical committee. Prior to the investigation, patients and healthy subjects gave their informed consent according to the Declaration of Helsinki.

**Results**

**Control subjects**

In all control subjects, stimulation of the infraorbital nerve on one side produced bilateral short latency responses in the unrectified averaged surface EMG. These evoked responses consisted of a positive or negative wave (Fig. 1) described with the mean latency preceded by lowercase letters indicating polarity (p19/n31). The mean (± SD) onset latency of the positive peak (p19) was 13.0 ± 1.2 ms for the SCM ipsilateral to the stimulus and 12.9 ± 1.1 ms for the contralateral SCM, and the peak latency of the positive wave was 19.0 ± 1.3 ms ipsilateral and 18.9 ± 1.4 ms contralateral to the stimulus. The mean latency of the negative peak (n31) was 30.4 ± 3.8 ms on the ipsilateral side and 29.8 ± 3.7 ms on the contralateral side. The mean square root of the ratio between the amplitude of the p19/n31 wave (peak to peak) and the mean rectified surface EMG activity preceding the stimulus was 1.13 ± 0.27 for the SCM ipsilateral to the stimulus and 1.12 ± 0.28 for the contralateral SCM. The lower confidence limit of the ratio between the amplitude of the p19/n31 wave and the mean rectified