Biocybernetics and Biomedical Engineering
2011, Volume 31, Number 3, pp. 3–17

Transcranial Magnetic Stimulation as a Tool for Brain Cortex Excitability Analysis in Migraine Pathophysiology

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Evidence is growing that neuronal excitability and responsiveness to sensory stimulation increase in migraine at cortical and brain stem levels. The perception of phosphenes induced by transcranial magnetic stimulation (TMS) allows analysis of visual cortex excitability during migraine attacks and interictal periods; TMS can also help assess prophylactic drug effects. The paper reviews studies of anticonvulsants and discuss the reduction of migraine frequency correlated inversely with an increase of phosphene thresholds and not correlated with motor thresholds. Multidisciplinary analysis along with TMS will aid our understanding of migraine mechanisms since most modern anticonvulsants have complex effects, not simply inhibition of cortical excitability.

K e y w o r d s: migraine, pathophysiology, cortex excitability, transcranial magnetic stimulation, evoked potential, electroencephalography, anticonvulsants

1. Introduction

Migraine is very common and is well known to every neurologist as a disabling disorder. However, the pathophysiology of migraine is complex and its etiology remains elusive. The first and oldest theory of the migraine mechanism, which appeared in the 1940s and 1950s, was based purely on a vascular theory. Wolff et al. concluded that intracranial vasoconstriction was responsible for the aura of migraine and that the subsequent vasodilatation and activation of perivascular noci-

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Received 23 November 2010; accepted 21 March 2011

ceptive nerves resulted in headache. The vascular theory has been based on the fact that: extracranial vessels become distended and pulsatile during a migraine attack, stimulation of intracranial vessels induces headache, and taking vasoconstrictors (ergots) improves the headache, whereas vasodilators (e.g., nitroglycerin) provoke and increase the attack. This theory has fallen out of favor and has been replaced by the neurovascular theory.

The current view is that migraine is a result of a complex series of neural and vascular events. It has been shown that a migraineur who is not having any headache can have neuronal hyperexcitability in the occipital cortex and sometimes in other cortical areas. The hyperexcitability exists not only in the attack but also during the interictal period; the brain is hypersensitive to different external stimuli, which can trigger migraine. These findings have been demonstrated in studies of the transcranial magnetic stimulation (TMS) and with the functional MRI and explain the special susceptibility of the migrainous brain to headaches. This observation suggested a parallel with epilepsy, since epileptics also have interictal neuronal irritability. Today migraine is considered as a disorder in which both neuronal and vascular components play a role in its pathophysiology. But it is clear that in migraine, vascular changes are more of an epiphenomenon.

2. Use of EEG in Migraine Studies

The absence of evident morphological changes placed the electrophysiological methods foremost in the clinical investigation of migraine; every attempt was made to show the neural basis of disturbed brain function in migraine. The introduction and widespread use of electroencephalography (EEG) led to anticipation that it would help to diagnose and distinguish between different types of migraine: migraine with aura (M+), migraine without aura (M–) and other primary headache disorders. Results of the EEG studies for the last half century have been disappointing and this method is no longer recommended for general practice as a diagnostic tool, however, some results have been important from a research point of view [1–4]. In some children there were reports of a slowing of generalized and focal background rhythms during migraine attacks [5, 6]. The “H-response” (the enhanced photic drive on EEG) was initially considered to be a distinctive characteristic of migraine [7], but later was revealed in other primary headache disorders [2]. Individual papers reported the disappearance of abnormal EEG rhythm after treatment with sumatriptan [8] or change after administration of flunarisine [9].

The development of more complicated mathematically-based EEG methods for brain mapping, the quantitative-topographical EEG (qEEG), led to their immediate use in migraine studies. The unilateral reduction of α-activity in M+ and children was demonstrated, chiefly within the first three days after the attack. Recently, qEEG in a longitudinal study of alpha peak frequency, variability, peak power and asymmetry

on pre-attack, attack and interictal days has shown increased frequency variability before the attack and increased peak power during the attack [10]. Several laboratories reported an increase in α-1 power, but other investigators showed the same tendency in control subjects [11]. A comparison of the qEEG changes in pre-ictal periods compared with headache-free period in 33 migraineurs and controls found that the patients had increased relative theta power in parieto-occipital, temporal and fronto-central areas and increased delta activity in the painful fronto-central region [12]. This double blinded controlled study revealed globally increased theta activity in migraineurs. EEG neither improves diagnostic accuracy nor convincingly identifies headache subtypes and is not a tool for structural causes of headache but does demonstrate obvious brain dysfunction not only during the attack but also in headache-free periods between the attacks. The best data for such an excitability come from studying of the aura.

3. Investigation of Neuronal Excitability in Aura and Migraine

Cortical spreading depression (CSD) is thought to be responsible for the migraine aura and for the headache itself. A wave of neuronal excitation in the cortical gray matter spreads from its site of origin at the rate of 2–6 mm/min and is followed by a wave of neuronal suppression. The blood vessels in this area dilate and then constrict. Therefore, the migraine aura is a cortical event with a well-defined neuroelectrical basis. PET scanning demonstrates that blood flow is reduced during a migrainous aura, but the spreading oligemia does not correspond to the vascular territories. The oligemia itself is insufficient to impair function. Instead, the flow is reduced because the CSD reduces metabolism.

There is a growing body of evidence demonstrating that neuronal excitability and responsiveness to sensory stimulation is increased in migraine at both cortical and brainstem levels. Subjective and clinically tested hypersensitivity of migraineurs to different environmental stimuli (especially to light and sound) confirm the idea of hyperexcitability of the cerebral cortex. However, findings concerning excitability of different neuronal structures analyzed with evoked potentials (EP) have been inconsistent [13, 14]. The variance and contradictions of observations among migraineurs in different studies might be technical, but could also be due to real changes in neural excitability over time.

3.1. Studies of Evoked Potentials

Studies of the cortical visual evoked potentials (VEP) have shown contradictory results. Some authors reported increase of the P1 and N3 amplitude [15], increase of the P1 latency to transient flash or pattern-reversal stimuli (PR-VEP) in M+ and M– during interictal period, while others reported no changes or opposite results

[16, 17]. With the PR-VEP during sustained sequential stimulation, migraineurs were characterized by a deficit in the physiological habituation: the normal amplitude reduction of the cortical response in the most patients was replaced by a potentiation or dishabituation, i.e. the amplitude was increased [18–21]. Rather than the result of structural impairment, the VEP habituation was mainly due to functional disturbances in two processing systems: the luminance-processing system and the contour-processing system [22]. Studies using visual and auditory cortical EP demonstrated that the deficit of cortical habituation in migraine normalizes following the preventive treatment [23]. The defective habituation can be also normalized in migraineurs by the repetitive high-frequency cortical TMS [14].

The contribution of VEP and brainstem auditory evoked potentials (BAEP) in understanding of the etiology and pathogenesis of migraine is very important despite the fact that for diagnostic purposes the evoked potentials are basically ineffective [13, 24, 25]. The phenomenon of abnormal habituation to repeated stimulation in migraine of both types (M+ and M–) was confirmed across all sensory modalities, reflecting the fact that neural dysexcitability is not limited by visual and/or auditory cortex structures. The dysfunction in cortical information processing was confirmed in the somatosensory cortex of migraineurs in adults as in children [26–28]. The importance of excitability changes was stressed by the efficacy of prophylaxis treatment. For instance topiramate and sodium valproate restore the cortical excitability to normal [28, 29].

Standard BAEP were widely investigated in migraine and only a single study reported increased latencies, especially for component V and mainly during the attack [30]. A more constant difference between migraine and control was found for amplitude habituation [31, 32].

Contingent negative variation (CNV), a slow negative cortical potential, has been recorded during a reaction time task. There are two main components: the early one indicates the expectation level and the later one signifies readiness. Like VEP and AEP, the CNV habituation was reduced in the migraine patients during interictal periods [33–37]. This observation is of special importance because the same abnormality was reported in healthy subjects in families with a history of migraine [37].

No functional impairment of the nociceptive pathways, including the trigeminal pathways, was found in the migraine patients, while the reduced habituation of laser-evoked pain potentials was shown [38, 39]. This finding probably reflects an abnormal excitability of the cortical areas involved in pain processing.

3.2. Use of Transcranial Magnetic Stimulation in Excitability Assessment

A new step in the analysis of brain pathophysiology in migraine was made after the introduction of non-invasive transcranial magnetic stimulation (TMS). TMS today is a tool of first choice to assess cortical excitability, and both motor and visual cortices have been explored [40]. In the migraine patients, TMS could test motor cortex

excitability (MEP thresholds), intracortical inhibition and facilitation, and cortical inhibition (cortical silent period).

In patients with lateralized migraine the interictal motor threshold (MT) significantly increased on the side of pain in patients with M+ ,yet on the pain free side of the head there was no difference of MT in comparison with controls [41]. There was also no difference between M– and controls. The abnormally high MT was reported by van der Kamp et al. [42, 43] during the pain-free period, the same as for the M+ and M– patients. The increased MT was also reported in the menstrual M+ [44]. In patients with M+, both three days before and three days after the attack the MT was significantly increased during the facilitation, while the MT at rest was normal; in patients with M– the MT was not changed at rest or in facilitation [45].

The analysis of cortical silent period (CSP), intracortical inhibition and facilitation exhibited no changes with the routine and paired TMS using round or figure-8 coils [46]. A statistically shorter CSP in hand muscles was found in 24 M+ patients [47]. It is important to mention that this TMS study was done 24 hours after the attack. Later the interictal excitability of cortical motor inhibitory interneurons in M+ and M– was defined more exactly when the CSP was tested from facial muscles [48]. The finding of a significantly shorter facial CSP silent period confirmed hypoexcitability of cortical inhibitory neurons in migraine patients. A paired TMS study published by Brighina et al. [49] reported the significant reduction of intracortical inhibition during the interictal period in patient with M+.

3.2.1. Phosphene Induction and Characteristics

Excitability of the visual cortex usually is assessed by the appearance and occurrence of the phosphenes (PH) induced by a single-pulse TMS (Fig. 1). The main parameters tested in TMS over visual cortex in the migraine patients are prevalence and the PH threshold. The following are features of phosphenes in migraine: they appear in the peripheral or central part of the visual field; different types never appear simultaneously; they have a bright central part; brightness increases with increased stimuli intensity; and evoked phosphenes do not repeat the visual migraine aura.

The prevalence of PH in M– did not differ in comparison to the controls, while in M+ the number of the migraine patients experiencing PH was significantly decreased [45]. The decreased PH prevalence in patients with M+ and M– was found by Mulleners et al. [50], but the results were not significantly different from the controls. Other authors reported opposite results: increased PH occurrence in M+ in comparison with the controls during the interictal period [47, 51, 52].

The analysis of PH threshold in migraine also revealed conflicting results at the outset. Some investigators found no changes in this parameter [45, 52] while most others established that in migraine the PH threshold induced by a single-pulse TMS decreased in comparison with controls (Table 1). Moreover, when PH was checked separately in the different types of migraine, in comparison with the control group

it was not only lower in the total group of migraine patients, but even statistically lower in M+ [47, 51, 53, 54].

Table 1. Phosphene thresholds (%) in control and migraine

Author	Control	M–	M+
Aurora et al., 1999 [47]	81	56	43*
Mulleners et al., 2001 [50]	66	46	47
Young et al., 2004 [57]	51	35	37
Gerwig et al., 2005 [56]	64	58	53*
Gunaydin et al., 2006 [54]	72	58	36*
Artemenko et al., 2008 [53]	63	56	49*

M– – migraine without aura; M+ – migraine with aura; * – $p < .05$ between M– and M+

Since the PH thresholds can be unstable, with some evolution over time, a fact which may play a role in the contradictory results – the thresholds were measured in some patients five times over 10 weeks [55]. There was no difference in the PH threshold evolution in the control and M– groups, but in M+ every other measurement was lower than the previous one. Evidently patients with M+ have a higher variability of PH threshold over time, revealing unstable excitability levels.

The abnormal excitability of the visual cortex in migraine became more obvious with the publication of an investigation with the paired TMS [56]. The single pulse stimulation was significant only between the patients with M+ and the controls. The paired TMS with the 50 ms interstimulus interval facilitated the primary visual

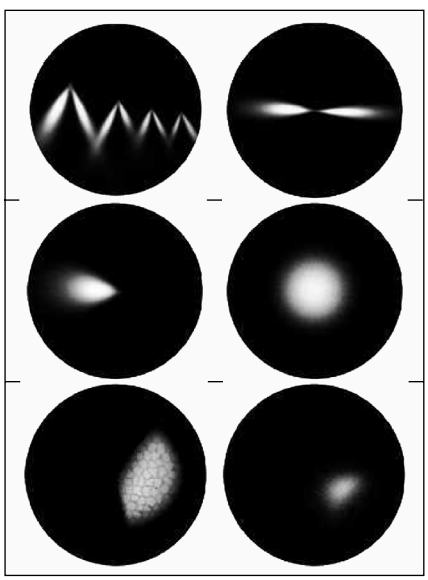

Fig. 1. Type of phosphenes in migraine simulated according to patients' description

cortex and the difference between PH in M+ and M– became equal and statistically significant in comparison to the controls. The paired TMS not only decreases the PH threshold, but also smoothes the variability in the migraine patients and the controls.

The establishment of occipital cortex excitability is very important for understanding the migraine pathophysiology. The PH threshold has shown the equal tendency to lower over time (TMS three times per week over three weeks) in patients with M+, M– and the menstrual migraine. The decline in the threshold levels for both migraine types from the first trial day to the last was impressive yet a question arose when the results were compared with the control group, since the controls had the same pattern of the threshold changes. The subjective component in reporting and discriminating phosphenes, as well as the learning effect, should be taken into account [57].

3.3. Repetitive Transcranial Magnetic Stimulation (rTMS)

A further technical development allowed repetitive TMS (rTMS) a role in the occipital cortex excitability as modified by different stimuli frequencies. In normal persons, rTMS with low frequency (1 Hz) for 15 minutes inhibited the underlying cortex and increased PH. A paradoxical effect of rTMS was reported in patients with migraine: 1 Hz rTMS over the occipital cortex led to a significantly increased visual cortex excitability expressed as a decrease in the PH threshold in subjects affected by M+ [52]. These facts suggest that the visual cortex hyperexcitability in migraineurs results from a deficiency of inhibitory circuits.

rTMS was used as a possible tool for modifying of cortical excitability in the analysis of habituation of PR-VEP in the migraine patients [58]. The deficient PR-VEP habituation in migraine was due to a reduced, and not to an increased pre-activation of the visual cortex. The role of abnormal inhibitory influence or changed habituation on hyperexcitability at the level of the occipital cortex was analyzed by employing magnetic suppression of perceptual accuracy (MSPA). In the migraine patients there was no MSPA suppression of the visual perception at any time interval of the TMS impulse [59]. The authors explained this as increased cortical excitability due to decreased cortical inhibitory mechanisms but not to a lack of habituation. This assumption was confirmed by the normalization of the MPSA pattern after treatment with 100 mg topiramate.

3.4. Results of Anticonvulsant Treatment

A growing evidence, as demonstrated with different neurophysiological paradigms, that the hyperexcitability of cerebral cortex plays a leading role in migraine pathophysiology makes it possible to use anticonvulsant drugs for migraine treatment in conjunction with other drugs. Migraine and epilepsy have been considered to

be closely related pathological conditions with possibly a common pathogenesis involving membrane excitability upon which anticonvulsant drugs can act [60, 61]. The symptomatic treatment of migraine was revolutionized by triptans, but in migraine prophylaxis anticonvulsants have gained primacy. Additional reports about the efficacy of anticonvulsants with a known mechanism of action would allow more precise speculation about the pathophysiology of the disease. Many good quality trials have reported at least a 50% reduction in the migraine frequency in trials comparing an anticonvulsant with placebo [62]. However, modern anticonvulsants used in the migraine prophylaxis treatment vary in their clinical efficacy and mechanisms of action (Table 2).

Table 2. Differences in the mechanism of action of anticonvulsants used in the migraine treatment

Medication	Voltage-gated Na+ channels blocking	L-type Ca2+ channels blocking	Negative modulation of glutamate receptors	Enhancement of GABA transmission	Inhibition of carbonic anhydrase
Topiramate	X	X	X	X	X
Valproate	X	X		X	
Gabapentin		X		X	
Lamotrigine	X	X			
Levetiracetam	mechanism of action is unknown				
Carbamazepine	X				
Oxcarbazepine	X	X			

In any study with anticonvulsants there is always a question whether the change in measured excitability observed after the prophylaxis treatment is a result of normal fluctuations in brain excitability rather than a response to the drug. Measurement of the occipital and motor cortex excitability before and after the treatment with certain anticonvulsants can help to understand the possible pathophysiological role of different parts of the brain in migraine.

Artemenko et al. found interesting results about the migraine frequency and the cortical excitability tested with TMS in patients with frequent migraine treated with topiramate [53]. The treatment with topiramate resulted in a significant decrease of the headache frequency, the migraine frequency, days with the acute migraine treatment, and amount of analgesic tablets used per month (Fig. 2–4). The mean number of the migraine days per month decreased from 12.0±1.3 per month to 8.9±3.2 per month ($p < 0.001$) during the first month and to 5.8±3.2 ($p < 0.001$) during the second month of the treatment (ANOVA $F = 62.6$, $df = 2$, $p < 0.001$). The mean difference was 6.2±3.5 days per month.

The TMS study showed that overall, treatment with topiramate resulted in an increase of the thresholds for MEPs as well as the thresholds for eliciting PH. The differences in the pre- and post-treatment thresholds were significant for both brain

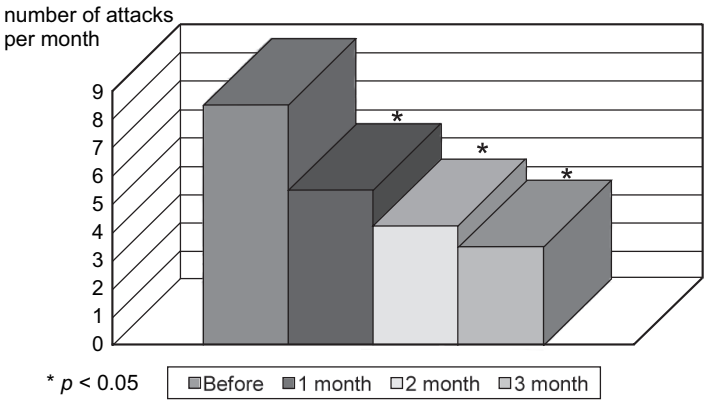

Fig. 2. Effect of topiramate: reduction of migraine frequency (n = 37)

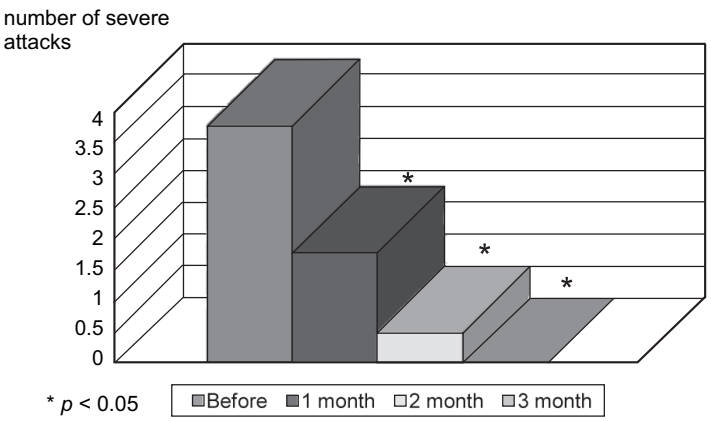

Fig. 3. Efficacy of topiramate: frequency of severe migraine attacks (n = 37)

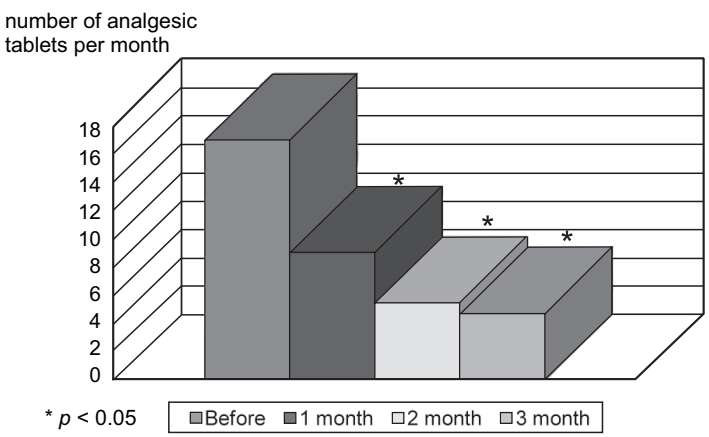

Fig. 4. Efficacy of topiramate: the use of acute headache medications (n = 37) MEP-Thr R/L – MEP threshold Right/Left hemisphere; PH-Thr – phosphene threshold

areas but were more pronounced for the PH thresholds (Fig. 5). The MEP thresholds were increased on average by 4%, which was consistent following right and left-sided stimulation, and the PH thresholds increased by 12%. There were no significant correlations between headache days and motor and the PH thresholds either at baseline or after topiramate withdrawal. Comparing changes in the headache days and changes in the thresholds, investigators found a significant inverse correlation between changes in the headache frequency and the PH thresholds (difference in headache days vs. visual thresholds, Spearman's rho = –0.553, $p = 0.002$) (Fig. 6).

Topiramate modulates the excitability of both motor and visual cortex in migraine and discloses in part the possible pathophysiological mechanism in migraine

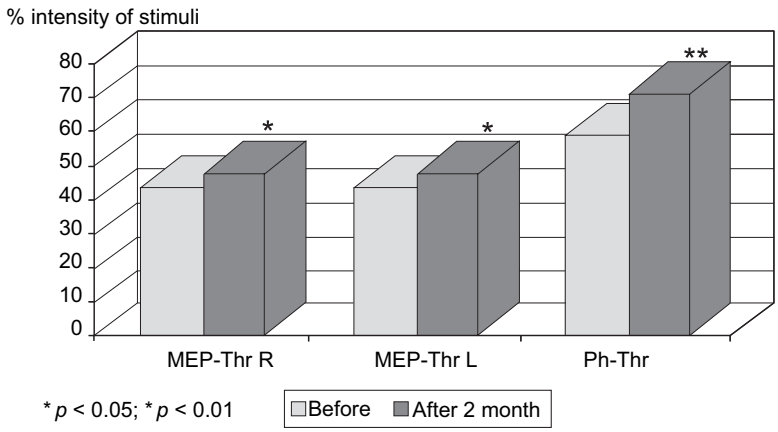

Fig. 5. TMS: cortical excitability in migraine without aura after topiramate treatment ($n = 37$)

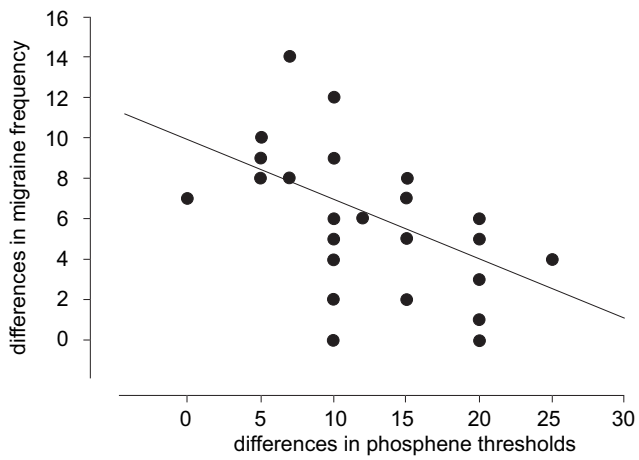

Fig. 6. Inhibitory effect of topiramate on visual cortex excitability established as the inverse correlations between migraine frequency and phosphene thresholds [from Artemenko et al., 2008]

and its prevention: the data clearly demonstrate the inhibitory effect of topiramate on the motor and visual cortical neurons. These findings are in line with the previous studies demonstrating the inhibitory/modulatory effect of topiramate on cortical excitability in healthy subjects probably via its GABAergic and/or glutamatergic mechanisms [63, 64, 65]. It seems interesting that administration of a single dose of topiramate (50–200mg) did not influence the motor thresholds [65], while in another study a chronic treatment over 6 weeks with a similar dosage resulted in a significant increase in the MEP- and PH-thresholds [53].

The migraine prophylaxis treatment with valproic acid established a weak correlation between clinical effects and decreased excitability of visual cortex only in patients with M+ ; the authors found an increase of the PH thresholds in patients with M+ [66]. A similar tendency in data to show a reduction in the migraine frequency with change in the PH threshold was demonstrated during the levetiracetam treatment [67]. The PH threshold increased during the treatment with levetiracetam at the 10% statistical level but not at the 5% significance level; the headache frequency and the PH-threshold were negatively correlated.

In the last paper reviewed, Aurora et al. demonstrated the effect of topiramate in migraine using an objective technique of magnetic suppression of perceptual accuracy (MSPA) [68]. There was no significant correlation between the headache frequency and change in inhibition of the occipital cortex.

4. Discussion

Despite contradictory results valproate sodium, topiramate and levetiracetam should be considered as neuromodulators with an independent effect on cortical excitability and responsiveness and with a possible influence on reducing migraine frequency. It is possible that a postulated relationship between migraine disease activity (headache frequency and severity) and cortical excitability is nonlinear with an initial slope and a subsequent saturation plateau at higher frequency of attacks, as in our sample. While considering the contradictions between results from different laboratories, one should pay attention not only to the recruited patient population and exact type of migraine but also to the stabilization of occipital cortex excitability at a certain level. A recent study demonstrated a higher intra- and inter-individual variability of the PH thresholds in the migraine patients compared to the healthy controls. Moreover, the highest and the lowest values were found to be possible predictors for subsequent migraine attack [55]. At the same time an absence of excitability fluctuations, changed by the prophylaxis treatment and the time to achieve it for the particular patient, can be more important than any other parameter.

For a more precise understanding of cortical excitability in migraine pathophysiology and its modulation in migraine prevention, it is necessary to study more prophylactic drugs and the relationship between cortical neurophysiology and clinical

effects. Although suitable biomarkers for migraine are missing, there are too many differences in research methodology and in the ongoing discussion of whether migraine is associated with cortical hypo- or hyperexcitability. Nevertheless it seems that TMS is still a promising tool for analysis of this mystery of nature.

5. Conclusion

The contradictory results in many papers already published, and likely in future papers, call for the following special requirements in the migraine investigation:

1) the necessity of carefully selecting of patients for inclusion in the study; the creation of a standard clinical protocol taking into account: different clinical forms, family history of the disease, prevalence or absence of phosphenes, different severity and different course of migraine, timing of the study in relation to attacks and phase of the menstrual cycle;
2) standardisation of the methodological and technical parameters of TMS;. type and size of coil, mono- or biphasic type of delivered impulse, impulse intensity and current direction should be uniform;
3) consideration of subjective components by the investigator, e.g., explaining to the patient how to recognise and discriminate phosphenes and assess pain status; and
4) development of original multidisciplinary analysis, which is necessary because the existing restricted methods can give only indirect information about the cause and effect of hyper- hypo-excitability of different structures of the migraine brain.

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