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REVIEW

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Cortical excitability in migraine

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Abstract Cortical hyperexcitability in migraine has been suggested to play a pivotal role in triggering migraine attacks, possibly via generation of spreading depression. Low levels of plasma, intracellular and brain magnesium as well as increased amplitudes of visual evoked potentials support this theory. More recent data on evoked and event related potentials, i.e. lack of habituation and low initial amplitudes during repetitive stimulation, however, may indicate reduced levels of cortical excitability. Transcranial magnetic stimulation of motor and visual cortices, a direct method to assess cortical excitability, yielded contradictory results. Lower or elevated motor thresholds, amplitudes and/or phosphene prevalence or even no significant differences at all were demonstrated suggesting also cortical hypo- rather than hyperexcitability in migraine. Methodological differences, selection of subjects, and timing of investigations might partly explain these marked differences. Clinical and genetic heterogeneity of migraine, for instance via opposite influence on neuronal excitability caused by recently described ion-channel mutations, might provide further explanation.

Key words Migraine • Excitability • Evoked potential • Transcranial magnetic stimulation • Biochemical data

Introduction

Migraine is a chronic, paroxysmal disorder, characterized by repetitive attacks of headache, nausea, vomiting, and photo- and phonophobia [1]. Any individual can suffer one or two migraine attacks in their lifetime [2] but more or less regular repetition of migraine attacks is regarded as a disease described as early as in the Egyptian times [3]. In recent years research on the pathomechanism of the migraine attack was stimulated by the introduction of selective serotonin receptor agonist drugs, the so-called triptans. Better understanding and, in parallel, more efficacious treatment of attacks have major importance for migraine sufferers. Another exciting issue of scientific research is the generation of repetitive attacks. A number of trigger factors for migraine attacks have been described previously but their mechanisms are still not clearly understood. Changes in cortical excitability might be a plausible explanation and, indeed, various studies of the visual system suggested cortical hyperexcitability of migraine patients between attacks [4–11]. Most recently, however, cortical hypo-, instead of hyperexcitability in the interictal period has also been demonstrated in some studies [12, 13]. Therefore, a review of current biochemical and electrophysiological data about cortical excitability in migraine seemed to be worthwhile.

Biochemical data

Serum, erythrocyte and saliva magnesium levels are reduced in patients with migraine with aura (MA) or without aura (MO) (Table 1) [14–17]. Lower magnesium levels

Table 1 Magnesium and neuroexcitatory amino acid levels in migraine patients compared to healthy controls

Substance	Sample	Patients	Reference
Magnesium ↓	Serum	MO, MA interictal	[14–19, 21]
	Erythrocytes		
	Mononuclear cells		
	Saliva		
	CSF		
	Brain		
Magnesium =	Serum	MO, MA interictal	[19]
	Whole blood cellular	MO, MA, FHM interictal	[20]
Glutamate ↑	Plasma	MO, MA ictal and interictal	[29, 30]
	CSF		
	Platelet	MA interictal	[31]
	Plasma	MO interictal	[31]
Glutamate ↓	Plasma	MO, MA ictal	[30]
	Plasma	Juvenile MO, MA	[32]
Aspartate ↑	Plasma	MO, MA ictal and interictal	[29, 30]
	CSF		
Aspartate ↓	Plasma	Juvenile MO, MA	[32]

MO, migraine without aura; *MA*, migraine with aura; *FHM*, familial hemiplegic migraine; *CSF*, cerebrospinal fluid

were also found in blood mononuclear cells which provide the most valid assessment of tissue magnesium stores [18]. Low levels of magnesium in cerebrospinal fluid (CSF) have been reported in migraineurs, but in the same study serum levels were normal [19]. On the other hand, Smeets et al. [20] failed to demonstrate any significant difference in whole blood cellular magnesium levels between groups of afflicted and non-afflicted members of 3 families with familial hemiplegic migraine (FHM), MO, MA and healthy controls.

Using 31-phosphorus magnetic resonance spectroscopy (^{31}P-MRS), a 20% decrease of brain magnesium was measured during a migraine attack and magnesium levels were lower, although not significantly so, in migraine patients studied between attacks [21, 22]. Welch et al. [23] were first to report a decrease of organic phosphates relative to inorganic phosphates (an index of phosphorylation potential in mitochondria) in the brain cortex using ^{31}P-MRS. These findings were confirmed and further extended to show reduced mitochondrial phosphorylation potential and energy reserve in the occipital cortex of MO and MA patients compared to healthy controls [24, 25]. This appears to be a generalized mitochondrial dysfunction in migraine, as it was also demonstrated in platelets and muscles [26, 27]. More recently, low brain magnesium, low phosphocreatine and high inorganic phosphate concentrations were demonstrated in juvenile MA patients between attacks [28].

Magnesium is essential for the energy transport of the cell and has major influence on membrane stability and as a consequence, on cortical excitability. Low levels of brain magnesium might therefore predispose the brain to spontaneous initiation of spreading depression (SD) or its activation via trigger factors. Neuroexcitatory amino acids and NMDA receptors may also be involved in SD generation and mediation. Elevated plasma levels of glutamate (GLU) and aspartate (ASP) were found in migraine patients between attacks and were further elevated during the attack [29]. Martinez et al. [30] found lower plasma and elevated CSF levels of the same amino acids in migraineurs during the attack. Between attacks, Cananzi et al. [31] found higher levels of platelet GLU in MA and of serum GLU in MO patients compared to healthy controls in adults, whereas D'Eufemia et al. [32] found lower GLU and ASP plasma levels and high erythrocyte/plasma concentrations of GLU and ASP in juvenile migraineurs. NMDA antagonists blocked or

suppressed spreading depression, and capsaicin induced c-fos expression in the trigeminal nucleus caudalis in animal models [33–35]. Interestingly, other compounds used either in the acute or prophylactic migraine therapy failed to reduce the propagation of SD in animal models [36].

Magnesium has been applied as a prophylactic drug in migraine and has been found to be effective in 2 double-blind, placebo-controlled trials with a therapeutic gain of 18.4% over placebo [37, 38], whereas in one trial no significant difference was found compared to placebo [39]. There are some early reports on the use of magnesium sulfate as an acute migraine treatment. Mauskop et al. [40, 41] found magnesium sulfate injection to be highly effective in attacks of migraine and cluster headache and also in tension-type headache and transformed migraine.

Psychophysical studies of the visual pathways

Migraine patients are more sensitive to environmental light stimuli [9, 10] and they report more intense illusions and more discomfort after visual stimulation with grating patterns than normal subjects (Table 2) [6, 7]. The latter abnormality may be more pronounced in MA than in MO [42]. Wray et al. [9] demonstrated that MA patients react faster in tasks reflecting low-level visual processing which might be related to visual hypersensitivity. Palmer and Chronicle [43] were not able to replicate their results using the same study design. In another study assessing the speed of visual processing in tasks of different complexity, no difference was observed in the accuracy rate or in the speed of response between MO and MA patients and controls [44]. Metacontrast masking is a paradigm critically dependent on inhibitory interactions in the primary visual cortex. In MA patients the masking function was significantly shallower, indicating cortical hyperexcitability [45]. Background grating hinders most MA patients in detecting a target letter [46] and subtle deficits in chromatic processing can be found in these patients [47].

Most of the abnormalities reported in migraine were more pronounced in MA and reflect dysfunctions at the cortical level, i.e. a hyperexcitability of the visual cortex. They might favor the hypothesis [48] that visual dysfunctions in migraine with aura are secondary to a loss of inhibitory GABAergic interneurons in the visual cortex due to repeated parenchymal insults during the aura, although these abnormalities were not more pronounced in patients with more frequent attacks or longer disease duration.

Table 2 Psychophysical studies in migraine patients

Method	Results	Patients	Reference
Questionnaire	↑ Sensitivity to environmental light stimuli	MO, MA	[10]
Visual stimulation with grating pattern	↑ Illusions and ↑ discomfort	MO, MA compared to HV	[7, 8]
	↑ Illusions and ↑ discomfort	MA compared to MO, HV	[42]
Tasks of low-level visual processing	Faster reaction	MA compared to HV	[9]
	No difference	MA, MO, HV	[43]
Tasks reflecting speed of visual processing	No difference	MO, MA compared to HV	[44]
Metacontrast masking	Shallower masking	MA compared to MO, HV	[45]
Target letter detection against background grating	Higher luminance needed for detection	MA compared to MO, HV	[46]
Detection of target orientation	↓ Speed for red line detection	MA compared to MO, HV	[47]

MO, migraine without aura; *MA*, migraine with aura; *HV*, healthy volunteers

Evoked and event-related potentials

Amplitudes of visual evoked potentials (VEP) were higher in MA and MO compared to healthy volunteers in a number of studies using flash or pattern-reversal stimulation [4, 5, 49–52]. Other groups failed to demonstrate any difference between migraineurs and healthy volunteers (Table 3) [53–56]. High amplitudes of averaged evoked potentials might however be a consequence of a deficit in the physiological habituation of responses shown during repetitive stimulations for VEP [57, 58], auditory evoked cortical responses [59] as well as event-related potentials, such as auditory novelty P3 [60], visual evoked oddball P3 [61] and contingent negative variation (CNV) [62, 63]. High VEP and CNV amplitudes decreased after prophylactic treatment with a betablocker [6, 62].

In children suffering from migraine, high amplitudes of VEP to flash stimuli [64] and CNV amplitudes [65, 66] as well as lack of habituation measured by P3 amplitude and latency [67] have been demonstrated.

During repetitive stimulation, a low amplitude of evoked cortical potentials after a small number of averagings or low intensity auditory stimulations was found in migraine patients interictally in several studies [57–59, 68, 69]. This might be due to a low preactivation level of sensory cortices [70] which can be caused by hypofunctioning state setting subcortico-cortical pathways [71, 72]. Moreover, a negative correlation has been demonstrated between initial VEP amplitude and its change during repeated stimulation in migraine patients and healthy subjects. By contrast, intensity dependence of cortical auditory evoked potentials (IDAP) is influenced by initial AEP amplitudes at low intensities only in migraineurs [68]. Taken together, these observations suggest that cortical preactivation levels are pivotal for the pathophysiological abnormalities found in migraine and low levels are in favor of a cortical hypoexcitability.

In addition, VEP and IDAP as well as CNV were found to undergo marked changes in temporal relation to the attack. Amplitudes tended to normalize during the attack [62], but they increased 2 days before the attack and returned to interictal levels during the days following the attack [69, 73, 74]. In most previous studies of evoked- or event-related potentials, the delay between the recordings and the next attack was not determined, which may in part account for the variability of findings.

Red light activates the visual cortex more strongly than other wavelengths [75]. For instance, red light but not light of other colors was able to trigger a photoconvulsive response in epileptic patients [76]. In a study of repetitive pattern reversal stimulations with the use of tinted glasses, healthy subjects showed a marked increase of VEP amplitudes to red light stimulation which was not found in migraine patients [13]. This lack of amplitude increase in MA patients might also indicate cortical hypoexcitability.

Transcranial magnetic stimulation

Transcranial electromagnetic stimulation (TMS) is an atraumatic and well-studied tool which is able to directly assess excitability of both motor and visual cortices as well as intracortical inhibition in the motor cortex when paired stimuli are applied with short interstimulus intervals [77, 78].

Studies using percutaneous magnetic stimulation of the motor cortex were performed in migraine patients, yielding

Table 3 Visual evoked potential amplitudes in migraine patients between attacks compared to healthy controls

Method	Results	Patients	Reference
Flash stimulus	↑ P1 amplitude	MO, MA	[49]
	↑ N3 amplitude	MO, MA	[4, 50]
Pattern reversal	No difference	MO	[53–56]
	↑ P100 amplitude	MO	[5, 6, 51]
	↑ P100 amplitude	MA (duration < 10 years)	[51]
	↑ P100 amplitude	MO, MA	[52]
	↓ P100 amplitude	MA (duration > 10 years)	[51]
Pattern reversal repetitive stimulation	Lack of habituation	MO, MA	[57, 58]

MO, migraine without aura; *MA*, migraine with aura

partly contradictory results. Maertens de Noodhout et al. [79] previously observed increased motor thresholds and electromyography (EMG) responses of smaller amplitudes after stimulation of the usually affected hemisphere in patients suffering from migraine with aura. Abnormally high motor thresholds were found bilaterally during and between attacks of menstrual migraine [80] as well as over the affected hemisphere in FHM [81]. By contrast, the latter group [82] had significantly increased amplitudes of EMG responses after motor cortex TMS in MO and MA and a positive correlation with attack frequency, but no motor threshold differences (Table 4).

My colleagues and I found that motor thresholds during isometric contraction were significantly higher in MA patients than in healthy controls, whereas no differences were found between migraineurs and healthy volunteers for motor thresholds at rest, maximal response amplitudes, MEP_{max}/M_{max} ratios or motor evoked potential modulation by conditioning stimuli with short interstimulus intervals [12].

Besides methodological differences, one has to take into account the timing of the recording in relationship to the attack to interpret these partly contradictory observations. The possible occurrence of an attack shortly after the recording was not monitored in Van der Kamp et al.'s study [82]. Modifications of motor cortex excitability around a migraine attack might have been a confounding factor in the latter study, especially since the MEP_{max}/M_{max} ratio increase observed by these authors was highest in patients with the most frequent attacks.

Excitability of the visual cortex can be estimated in individual subjects by determining the TMS threshold for phosphene induction, and group differences can be sought by assessing the prevalence of phosphenes at maximal stimulator output [83]. Aurora et al. [84, 85] found that a significantly higher proportion of migraineurs experienced phosphenes and the probability of triggering an attack in migraineurs was higher than in controls (Table 5). They concluded that excitability of the visual cortex to TMS is increased in migraine with aura. Aguggia et al. [86] were not able to detect any difference in phosphene prevalence between MA, tension-type headache patients or healthy controls, whereas the threshold of phosphene generation was significantly lower in MA. As a striking difference to these findings [84–86], we demonstrated significantly lower prevalence of phosphenes in migraine with aura after occipital TMS without any significant threshold differences [12].

The reason for this may be multiple; first of all, methodological differences cannot be excluded. Patient selection might be an explanation, as patients were selected according to their propensity to having attacks triggered by visual stimuli in Aurora et al.'s study (personal communication) but not in ours. Another interesting factor is the low prevalance of phosphenes in the control group (25%) in Aurora et al.'s study which was not the case in the other studies cited (89% and 100%).

Table 4 Transcranial magnetic stimulation of motor cortex in migraine patients compared to healthy controls

Method	Results	Patients	Reference
Threshold	↑ Over usually affected hemisphere	MA interictal	[79]
	↑ Bilaterally	Menstrual migraine ictal and interictal	[80]
	↑ Over the affected hemisphere	FHM interictal	[81]
	↑ During isometric contraction	MA interictal	[12]
Amplitudes (MEP_{max}/M_{max} ratio)	↑ Bilaterally	MO, MA interictal in positive correlation with attak frequency	[82]
	No difference	MO, MA interictal	[12]
Paired stimulation with short interstimulus interval	No difference	MO, MA interictal	[12]

MO, migraine without aura; *MA*, migraine with aura; *FHM*, familial hemiplegic migraine

Table 5 Trancranial magnetic stimulation of occipital cortex in migraine patients and healthy volunteers

Method	Results	Patients	Reference
Phosphene prevalence	27% in HV 100% in MA	11 MA 11 HV	[84]
	25% in HV 87% in MA+MO	8 HV 1 MO 14 MA	[85]
	89% in HV 82% in MO 56% in MA	19 HV 22 MO 18 MA	[12]
	100% in HV 100% in MA 10 HV	10 MA	[86]
Threshold for phosphene generation	↓ in MA	3 HV 11MA	[84]
	↓ in MA	2 HV 13 MA	[85]
	No significant difference	17 HV 18 MO 10 MA	[12]
	Significantly ↓ in MA	10 HV 10 MA	[86]

MO, migraine without aura; *MA*, migraine with aura; *HV*, healthy volunteers

Conclusions

Biochemical and electrophysiological data reviewed in this article do not unanimously favor cortical hypo- or hyperexcitability in migraine. Low magnesium levels, reduced mitochondrial energy reserves and elevated levels of neuroexcitatory amino acids might suggest cortical hyperexcitability. However, therapeutic trials with magnesium show low efficacy rates, which does not indicate a major role of magnesium in attack generation. Electrophysiological data are even more contradictory. Some of these contradictions can be explained by recent findings, like lack of habituation of evoked and event-related potentials between attacks and their marked changes in the peri-attack period which were not taken into account in previous studies. Most striking differences are presented in studies using transcranial magnetic stimulation. Besides methodological differences, selection of migraine patients and controls and timing of investigations might provide some explanation. Migraine is undoubtedly heterogenous from both clinical and pathophysiological points of view. It is most probably a polygenic disorder and the weight of the various genes might also differ between patients [87]. The only gene that has been hitherto identified codes for the alpha subunit of a P/Q calcium channel (CACNL1A4) and may contain various missense mutations or deletions [88]. Depending on the site of the mutation within the gene, the functional consequence on the ion channel is either a loss or a gain in function [89, 90]. Such mutations will exert opposite influences on cortical neurons.

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