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REVIEW

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Exciting excitable brains: an update on migraine pathophysiology

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Abstract This last decade has seen remarkable progress made towards unraveling the mystery of primary headache disorders like migraine and cluster. The vascular theory has been superseded by recognition that neurovascular phenomena seem to be the permissive and triggering factors in migraine and cluster headache. This understanding has been achieved through new imaging modalities such as positron emission tomography and functional magnetic resonance imaging. Prior to these imaging techniques it was impossible to study the primary headache disorders because these had no structural basis. There is now an increasing body of evidence that the brain is involved primarily in cluster and migraine and that vessel dilatation is an epiphenomenon.

Key words Migraine • Hyperexcitability • Imaging

Introduction

The exact pathogenesis of migraine remains to be determined. The pendulum for concepts of migraine pathophysiology swung between primary vascular and primary neural mechanisms. Harold G. Wolff, a pioneer of the vascular theory of migraine, proposed that the neurological symptoms of the migraine aura were caused by cerebral vasoconstriction, and the headache by vasodilatation [1]. Lashley's experience [2] of his own visual aura led him to the concept of the spreading cortical depression (SCD) of Leao being the primary cause, thus promulgating the neural theory of migraine [3]. Newer imaging techniques have made it possible to study the very early events of migraine, thus both theories have been reconciled by contemporary proponents of a neuro-vascular mechanism of the migraine attack. There is an increasing body of evidence for an inherited disorder that occurs in susceptible individuals, and for the concept of central neuronal hyperexcitability as a pivotal physiological disturbance predisposing to migraine [4]. The reasons for increased neuronal excitability may be multifactorial. Most recently, abnormality of calcium channels has been introduced as a potential mechanism of interictal neuronal excitability [5]. Mutant voltage-gated P/Q type calcium channel genes likely influence presynaptic neurotransmitter release, possibly of excitatory or inhibitory amino-acid systems. It can therefore be hypothesized that genetic abnormalities result in a lowered threshold of response to trigger factors.

Migraine is an episodic disorder involving head pain and cortical phenomena without structural abnormalities. Therefore, only investigations aimed at studying the function of the brain provide insight into migraine pathophysiology. In this paper first the mechanism of aura and head pain are discussed, followed by a discussion of interictal disturbances which lead to a propensity to developing migraine.

Mechanisms of aura

The unpredictable and elusive nature of migraine has prevented many investigators from systematically studying migraine aura. A recent study by Cao et al. [6], wherein migraine was reliably visually triggered in 50% of subjects, enabled the immediate early events of the migraine attack to be measured for the first time. A red and green checkerboard was used for visual stimulation since migraineurs are known to be sensitive to linear stimuli. Using the recently developed blood oxygen level-dependent functional magnetic resonance imaging (fMRI-BOLD) technique, the authors were able to measure, with millimeter resolution, second-to-second activation of occipital cortex to visual stimulation in subjects with migraine. None of six normal controls developed a headache and all displayed normal patterns of BOLD signals on visual activation. Six patients with migraine with aura (MwA) and two patients with migraine without aura (MwoA) experienced visually triggered headache; two also had accompanying visual change. Headache was preceded by suppression of initial activation that slowly propagated into the contiguous occipital cortex at a rate of 3–6 mm/min. This neuronal suppression was accompanied by an increase in baseline contrast intensity, indicative of vasodilatation and tissue hyperoxygenation. The baseline contrast increases that indicated tissue hyperoxygenation were similar to those witnessed in experimental spreading cortical depression (SCD) [7]. These spreading events accompanied visually triggered headache whether or not it was associated with visual change. In this study patients were selected based on a history of visually triggered headache, so that generalizing these findings to all migraine patients must be done with caution. Nevertheless, previously hypothesized mechanisms of SCD in migraine were clarified by this study, and the previously controversial findings of ischemia accompanying migraine aura were not supported. Recently, a spontaneous migraine with aura has been described by Hadjiakani et al. [8] with similar changes on BOLD-fMRI as described by Cao et al. [6].

Perfusion-weighted imaging (PWI), another novel functional neuroimaging technique particularly suited to study short-lived events such as migraine aura, has been used to study 19 patients during spontaneous migraine [9]; 28 attacks were studied because some patients were imaged more than once. There was a relative reduction of cerebral blood flow in the occipital cortex contralateral to the visual defect during MwA, but this was observed only in the occipital cortex and not in other brain regions. One subject with attacks of both MwA and MwoA demonstrated these phenomena only during MwA. No significant changes in blood flow were observed in MwoA. The hemodynamic changes were demonstrated only on PWI and not on diffusion-weighted imaging (DWI); DWI is sensitive to ischemia and thus further supports MwA not being an ischemic event.

These imaging studies, albeit in favor of the neural basis of migraine, are not able to demonstrate SCD, the putative mechanism of migraine aura. To date, SCD has been recorded successfully in animal models only [10]. In animals, the SCD's band of hyperexcited neurons travels into sulci or fissures, eliciting a magnetoencephalographic signal. Using 7-channel magnetoencephalography (MEG), Barkley et al. [11] observed DC shifts in spontaneous migraine. A further study of a larger number of patients has not been possible because of the unpredictable nature of migraine and time of capture of these spontaneous events. Using the visual trigger modeled by Cao et al. [6], Bowyer et al. [12] have now been able to detect DC shifts when headache or aura was precipitated. These studies were performed using whole head MEG, which permits precise localization of signals. In this study headache was triggered in 5 of 8 migraine patients and in none of 6 controls. DC-MEG shifts were observed in migraine subjects during visually triggered aura and in a patient studied during the first few minutes of spontaneous aura. No DC-MEG shifts were seen in control subjects. This is additional evidence supporting the primary neural basis migraine and confirms MEG-recorded DC shifts typical of those found during SCD, reported previously in migraine attacks.

Mechanism of pain

The brainstem and specifically the trigeminovascular system have been implicated in playing a large role during a migraine attack from recent experimental and clinical data [13]. It is hypothesized that a sterile inflammatory response occurs due to the release of neuropeptides, i.e. calcitonin gene related peptide (CGRP), neurokinin A and substance P [14]. The development of novel antimigraine drugs for the treatment of migraine has been based predominantly on these animal models. This mechanism is further strengthened by the discovery of binding sites for the $5HT_{1B/1D}$ agonists on brainstem structures [14–16]. The first human study to show activation in the brainstem used positron emission tomography (PET) performed in subjects during spontaneous migraine. Because PET lacks sufficient resolution for exact anatomical localization, the activation was hypothesized to be in the regions of dorsal raphe nuclei (DRN), periaqueductal gray (PAG) and locus ceruleus (LC) [17]. Recently an isolated case report found red nucleus (RN) and substantia nigra (SN) to be activated in a spontaneous migraine attack [18]. The same authors also reported the RN and SN to be activated in the subjects with visually triggered migraine [19]. The RN and SN are best known for their functional roles in motor control. The RN however has also been associated with pain

and nociception [20]. Numerous animal studies have documented a response of RN neurons to a variety of sensory and noxious stimuli. In a PET study performed on normal volunteers during capsaicin-induced pain, ipsilateral activation of RN was documented. It remains to be clarified whether or not the RN is involved in the pain pathways or in the motor response to pain.

Evidence of interictal disturbances

Electroencephalography (EEG) was one of the first techniques undertaken to discern physiological differences between migraine and controls. A recent review suggests that EEG is not valuable as a diagnostic tool for primary headache disorders [21]. The enhanced photic drive response on the EEG H-response, which was thought to be characteristic of migraine [22], has recently been confirmed by spectral analysis [23, 24]. The specificity of the H-response, however, has been questioned since it may occur with other primary headache disorders [21]. Abnormal steady state response evoked by a sine-wave visual stimulus (SVEP) was seen in migraineurs, and improved after administration of propranalol [25, 26]. Finally, following a repetitive pattern-reversal stimulation, migraineurs but not controls displayed potentiation of VEP amplitude that reached its maximum in the second to fourth blocks [27]. Similar results were seen using prolonged stimulation [28]. More recently, however, and in agreement with visual evoked potentials (VEP) studies, strong interical dependence of the auditory evoked potentials (AEPs) on stimulus intensity was demonstrated in migraine [29]. Furthermore, the response was modulated by zolmitriptan [30].

Transcranial magnetic stimulation (TMS) has been developed to noninvasively study cortical physiology [31, 32], and this technique is now increasingly being used to study migraine.

TMS of motor cortex in migraine

Several studies have investigated the motor cortex of migraineurs using TMS. Three studies have been performed on the motor cortex, two of which reported increased excitability in migraineurs and suggested that this neurophysiological correlate may have a role in migraine mechanisms [33, 34]. The first study compared subjects with migraine with and without aura to controls, and demonstrated an increased motor threshold in classic migraine [33]. The motor threshold was increased on the side corresponding to the aura. The threshold difference could not be attributed to attack frequency. The second study was performed on menstrual migraineurs during the cycle compared to controls [34]. An increased threshold was demonstrated, similar to the first study, but in this study the patients had migraine without aura.

Following these studies, two other studies were performed. In the first study there was a difference in amplitude of motor evoked potentials (MEPs) in migraine with aura compared to controls, but no difference in motor threshold [35]. The differences between this study and previous reports of increased threshold were explained by the authors on the basis of attack frequency, which was higher in their group of patients.

In a second study of familial hemiplegic migraine, the threshold of motor cortex was higher on the side corresponding to the aura [36]. Using paired pulses a recent study demonstrated reduced motor cortical excitability after administration of zolmitriptan, a centrally acting $5HT_{1B/D}$ used in the treatment of migraine [37]. This technique thus provides a new opportunity to study cortical physiology and the effects of drugs in migraine.

Cortical silent period in migraine

Two studies have examined the cortical silent period (CSP). Although the results were judged to be preliminary, both reported no differences in CSP at high levels of stimulus intensity [38, 39], but at low stimulus intensity a shorter CSP was documented in migraine with aura compared to controls [39]. Since CSP, in part, is a measure of central inhibition of motor pathways, this shortening of the CSP suggests reduced central inhibition, inferring increased excitability.

TMS of occipital cortex in migraine

Using TMS to study the occipital cortex is perhaps more relevant to migraine because enhanced excitability of the occipital cortex may underlie either spontaneous or visually triggered migraine aura [4]. Occipital cortex excitability in migraine has been evaluated by the generation of phosphenes during TMS of occipital cortex. The first study reported a low threshold for generation of phosphenes in subjects with MwA, inferring hyperexcitability of the occipital cortex [40]. In contrast, occipital cortex hypoexcitability was reported in MwA based on a lower prevalence of phosphenes stimulated by TMS [38]. Important technical differences, such as the type of stimulator or coil size, might explain these conflicting findings [41]. Since these early reports, there have been two more studies performed on the occipital cortex using

TMS, both confirming the initial reports of hyperexcitability [42, 43]. In one of these, hyperexcitability of the occipital cortex was associated with a propensity to visually triggered headache in the same patients [43]. Recently Battelli and colleagues investigated the extrastriate visual area V5, which is important for the perception of motion [44]. Both migraine with and without aura groups required significantly lower magnetic field strength for the induction of moving phosphenes, as compared to the control group; this difference was significant for V5 in both left and right hemispheres. In addition the phosphenes were better defined and had clearer presentation in migraine groups, whereas in controls they tended to be more transient and ill-defined.

Repetitive TMS (rTMS) has also been used to study brain physiology in migraine. In healthy normal subjects, a few minutes of low-frequency rTMS (about 1 Hz) appears to reduce cortical excitability for a few minutes after stimulation, whereas cortical excitability is increased after higher-frequency rTMS (more than 5 Hz) [45]. Bohotin et al. [46] used an interesting design in which a widely used measure of visual system function, the pattern-reversal visual evoked potentials (PR-VEP), was recorded before and after both 1-Hz and 10-Hz rTMS in migraine without aura, migraine with aura, and normal control groups [46]. In both migraine groups, the PR-VEP amplitude was greater after 10-Hz rTMS (900 pulses in total), whereas PR-VEP amplitude was unaffected by 1-Hz rTMS. By contrast, in the control group, PR-VEP amplitude was decreased after 1-Hz rTMS and unaffected by 10-Hz rTMS. Bohotin et al. [46] further demonstrated that an abnormal pre-rTMS habituation of PR-VEP amplitude was normalised in both patient groups after 10-Hz rTMS; 1-Hz rTMS, by contrast, did not alter the abnormal habituation. A second study by Brighina et al. [47] demonstrated reduction in inhibition in migraine using the effect of rTMS on phosphene threshold. They demonstrated a reduction in phosphene threshold in controls but not in migraine after 1-Hz rTMS. Thus they once again inferred cortical hyperexcitability in migraine.

Conclusions

We currently conceive of a migraine attack as originating in the brain. Triggers of an attack initiate a depolarizing neuroelectric and metabolic event likened to the spreading depression of Leao. This event activates the headache and associated features of the attack by mechanisms that remain to be determined, but appear to involve either peripheral trigeminovascular or brainstem pathways, or both. Excitability of cell membranes, perhaps in part genetically determined, is the brain's susceptibility to attacks. Factors that increase or decrease neuronal excitability constitute the threshold for triggering attacks.

Using a model of visual stress-induced migraine or by studying spontaneous attacks, and applying advanced imaging and neurophysiological methods, results have been obtained that support spreading neuronal inhibition as the basis of aura. This neuroelectric event is accompanied by hyperoxia of the brain, possibly associated with vasodilatation. Evidence has been obtained also that the spreading cortical event can activate subcortical centers possibly involved in nociception and associated symptoms of the migraine attack. Susceptibility to migraine attacks appears related to brain hyperexcitability. These newer techniques of functional neuroimaging have confirmed the primary neural basis of the migraine attack with secondary vascular changes, reconciling previous theories into a neurovascular mechanism.

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