

Giorgio Sandrini
Alberto Proietti Cecchini
Sonya Ivanova Hristova
Grazia Sances
Giuseppe Nappi

Neurophysiology of migraine

G. Sandrini (✉) • A. Proietti Cecchini
S.I. Hristova • G. Sances • G. Nappi
Psychophysiology of Pain Laboratory,
University Centre for Adaptive Disorders
and Headache (UCADH),
IRCCS C. Mondino Foundation,
Department of Neurological Sciences,
University of Pavia,
Via Palestro 3, I-27100 Pavia, Italy
e-mail: gsandrini@unipv.it
Tel.: +39-0382-380279
Fax: +39-0382-380286

S.I. Hristova
University Neurological Hospital, Sofia,
Bulgaria

G. Nappi
Institute of Nervous and Mental Diseases,
La Sapienza University of Rome, Rome, Italy

Abstract We review the main electrophysiological abnormalities emerging from migraine studies and discuss them from the pathophysiological point of view. Considerations range from genetic aspects to the heterogeneous clinical phenotype of migraine.

Key words Migraine trait • Cortical excitability • Trigeminal reflex • Habituation • Trigeminovascular system

Introduction

Migraine is a chronic paroxysmal disorder characterised by headache attacks associated with autonomic symptoms. Due to its chronic course, its genetic transmission and the considerable disability induced, migraine is regarded as an out-and-out disease.

Experimental evidence of recent years has led to the current opinion that both vascular and neuronal factors, closely related, are important in the pathophysiology of migraine [1].

Migraine attacks seem to result from pathophysiological mechanisms activated by specific trigger factors. The recur-

rence of migraine attacks may depend either on a reduced threshold or on particularly strong or frequent trigger factors, or both.

The migraine trait

A genetic predisposition to migraine determines individual attack thresholds. However, on the basis of migraine concordance rates between monozygotic twins, it is thought that, due to favourable environmental conditions, at least 50% of those who have a genetic disposition to migraine will never experience a migraine attack during their lifetime.

By contrast, in the other half of genetically potential migraineurs, the migraine disorder will appear as a consequence of the intervention of concurrent factors, which enhance the genic penetrance of the disease and account for the great clinical heterogeneity seen among migraine patients [2].

Indeed, a series of environmental determinants – mostly unknown – will exert a modulatory effect on the inherited vulnerability. They may act, permanently or for long periods of time, in a complex gene-environment interaction that influences genic penetrance and phenotypic expression according to sex, age, lifestyle, neuroendocrine activity, etc.

Against this background, i.e. the so-called migraine trait, precipitating or favourable factors, external and internal, such as hormonal fluctuations, the sleep-wake cycle, psychosocial factors (e.g. stress-relax cycle, anxiety-depressive disorders), vasoactive substances and painkiller (mis)use will occasionally act, causing the migraine attack threshold to be crossed, triggering the recurrence of attacks, and accounting for the extreme variability over time.

The hypothetically intrinsic nature of the condition predisposing to migraine attacks supports the fundamental importance of the congenital abnormality in habituation mechanisms to physiological changes and, in particular, to sensory stimuli. The abnormal sensory habituation found in migraineurs is thought to depend on dysfunction of the aminergic pathway control on sensory information processing.

The putative role of a genetic factor in migraine is further supported by a recent study in which single fibre electromyography (SFEMG) was used in subjects affected by migraine with aura. In this study, subclinical functional abnormalities of the neuromuscular junction were documented in a subgroup of patients, suggesting altered function of the P/Q calcium channels, which are particularly represented at the neuromuscular junction level [3].

Cortical disexcitability and metabolic derangement

Biochemical, neurophysiological and neuroimaging (spectroscopic MRI) studies all define migraine as a disorder characterised by cortical disexcitability, documented in migraine patients during the interictal period [4].

Cortical disexcitability is thought to depend directly on a genetically determined ion channel dysfunction [5], which causes a neuronal instability that accounts for the evidence, in evoked potential studies, of reduced threshold, increased amplitude of cortical responses and lack of habituation to repeated stimuli.

In fact, a number of neurophysiological studies on cortical evoked potentials have shown increased amplitude of visual evoked responses [6] and of cognitive evoked potentials (CNV, P300), with defective habituation patterns during both visual and auditory stimulations [7]. The normalisation occurring following prophylactic beta-blocker therapy [8] suggests that the deficient habituation might reflect an abnormal noradrenergic arousal, determining a state of cortical hyperexcitability [9].

Transcranial magnetic stimulation (TMS) is a safe and noninvasive technique, widely used in studies on corticospinal function and on corticocortical inhibition-facilitation mechanisms assessed also with pharmacological modulation. To date, TMS studies have produced conflicting data [10]. These studies have been carried out either by stimulating the motor cortex and recording the muscular response [11], or by stimulating the visual cortex and reporting the subjective perception of phosphenes [12]. In both cases, the threshold for inducing a peripheral, visual or motor response has been taken as an indirect index of cortical excitability. While increased motor and visual cortex excitability in migraine [4], more evident in migraine with aura, is generally recognised, the study by Afrà et al. [13] showed, on the contrary, a condition of hypoexcitability in migraine with aura, without any significant difference between controls and patients with migraine without aura. There are a number of misleading factors that may possibly account for this discordance: differences in the samples of migraine patients, not only in terms of disease duration and severity (frequency and severity of attacks), but also in the interval between the recording session and the previous and successive attacks. Moreover, in the female subgroup, it is important to know the concomitant menstrual cycle phase, since central nervous system (CNS) excitability is strongly influenced by menses [14].

The neurophysiological basis of abnormal neuronal excitability in migraine subjects lies in such combinations of intrinsic neuronal instability with other biochemical alterations, i.e. defective mitochondrial oxidative phosphorylation mechanisms with consequent alteration of energy metabolism [15], low levels of intracellular magnesium [16], dysfunction of the GABAergic system and excess of excitatory amino acids [17].

Moreover, a recent biochemical study showed a reduced activity of Gi proteins in headache subjects suffering from migraine or cluster headache, together with 4-fold elevated levels of adenosine cAMP compared to controls [18]. Since Gi protein activation reduces cell excitability and cAMP has a vasodilator effect, the authors suggest that these data may represent the biological basis for the neuronal hyperexcitability observed in migraine, which in turn accounts for the observed hypersensitivity to environmental stimuli.

Trigeminovascular hypothesis and central sensitisation

Several lines of evidence point to the activation of the trigeminovascular system as the common final pathway of the clinical expression of pain in a migraine attack (Fig. 1). This activation may take place in migraine subjects through cortical spreading depression-like phenomena, as documented in experiments conducted in animal models [19]. Moreover, systemic administration of nitroglycerin (a donor of nitric oxide) in the rat specifically and selectively activated areas of the brainstem and midbrain implicated in the processing of nociceptive information and in the integration of vegetative and neuroendocrine responses [20].

In order to explore brainstem function, trigeminofacial reflexes have been investigated in headache patients. A few studies have shown asymmetry of reflex responses and other minor abnormalities.

We recorded electrically elicited corneal reflexes in patients with side-locked migraine and compared them to those of migraine patients with side-shift migraine and controls. In unilateral migraine, reflex and pain threshold parameters were lower on the symptomatic side than on the contralateral side, and significantly lower than those found in migraine with side-shift or in controls. These data are in keeping with the findings of corneal reflex in cluster headache, another neurovascular primary headache in which the reflex threshold during the active phase was reduced on the symptomatic side while normal values were reported during the remission period [21]. Furthermore, these data point to an abnormal trigeminal sensitivity that is more marked on the side where the pain recurs.

Studies on the blink reflex in migraine have failed to provide consistent data. Due to the nociceptive nature of the R2 and R3 components of the blink reflex, they have recently received major attention. Some authors have found a

reduced threshold for the R3 component in migraine subjects, who had an early R3 appearance, close to the R2 threshold [22]. However, the neural circuits of this ultra-late component of the blink reflex, which is probably part of the startle reaction, are still being debated.

The counterpart of nociceptive brainstem reflexes at spinal level is the biceps femoris muscle flexion reflex, the RIII reflex, which has been explored in several pain disorders and in primary headache [23]. This electrophysiological method allows the assessment of central pain processing, since the reflex is modulated by serotonergic and opiate fibers descending from the nucleus raphe dorsalis and the periaqueductal gray (PAG) in particular. In a study of migraine subjects, the major finding was a decreased RIII reflex threshold proportional to headache severity; the RIII reflex was reduced only in severe forms of migraine [24].

Activation of the trigeminal sensitive afferents is associated with the local release of neuropeptides that leads to vasodilation (calcitonin gene-related peptide, CGRP) and to the increase in vascular permeability seen in so-called neurogenic inflammation (substance P, neurokinin A), accompanied by platelet and mast cell activation.

The release of CGRP, verified also in man by blood taps from the jugular vein during migraine attacks [25] and cluster headache, supports the hypothesis that trigeminovascular activation is responsible for the subsequent biochemical and intra- and extracranial blood flow modifications, which are followed by the triggering of nociceptive impulses along the visceral afferents that run to the trigeminal nucleus caudalis.

It appears, therefore, that the trigeminovascular hypothesis advanced by Moskowitz [26] sums up the vascular theory previously developed by Wolff [27], no longer tenable due to evidence that migraine is not provoked simply by vasodilation mechanisms, and gives support to Sicuteri's [28] central disinociceptive theory.

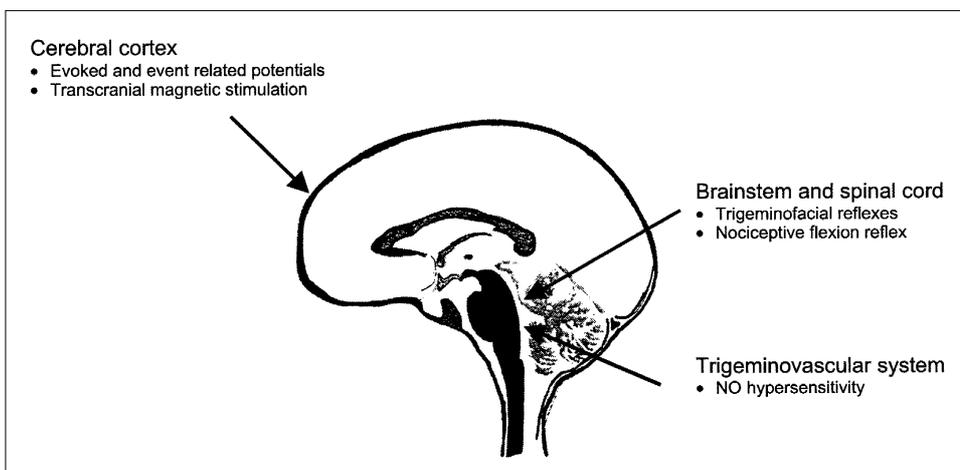


Fig. 1 CNS structures putatively involved in the pathophysiology of migraine, as suggested by electrophysiological and pharmacological evidence. *NO*, nitric oxide

The convergence of the visceral (intracranial) and somatic (extracranial) afferents on the trigeminocervical complex also accounts for the pain reported in the area of the upper cervical roots and the increased sensitivity of the pericranial structures. As shown in studies by Burstein et al. [29], a condition of cutaneous allodynia ipsilateral to the pain may occur during migraine attacks, and may persist for a long time, several hours or days, even persisting in the interictal period.

Recurrence of attacks may, therefore, lead to sensitisation of the trigeminal and trigeminocervical neurons, with an enlargement of the receptive fields to the pericranial areas associated with a lowering of the activation threshold of the nociceptive terminals, either peripheral cutaneous or perivascular meningeal.

The importance of brainstem mechanisms in the pathogenesis of migraine attacks has been demonstrated in a PET study [30] of subjects during spontaneous migraine attacks. Evidence of brainstem activation contralateral to the pain side has been found, referred to the periaqueductal grey (dorsal raphe nucleus) and to the dorsolateral part of the pons (locus coeruleus). The locus coeruleus, the main noradrenergic nucleus of the CNS, exerts not only an action of vasoconstriction on the cerebral blood flow but also a mod-

ulatory action on the permeability of the blood-brain barrier. It is also involved in sensory information processing in the regulation of the signal-to-noise ratio, in concert with serotonergic tone, mainly sustained by the dorsal raphe nucleus.

Abnormalities in neurovascular and autonomic modulation activities by these and other functionally correlated brainstem and midbrain nuclei explain many, if not all, of the features present in a migraine attack.

It is thought that the symptomatic treatment of attacks, for example with the use of triptans, targets the trigeminovascular system as responsible for the clinical expression of the pain, while prophylactic action acts on the CNS and, finally, on the midbrain-brainstem "generators" or "modifiers" of the migraine attack threshold.

Conclusions

Migraine is currently considered to be a complex disease characterised by a genetically determined instability in the control systems of sensory information processing that renders the subject vulnerable to the trigger factors and that appears primarily as a neurovascular dysfunction.

References

- Schoenen J (1998) The pathophysiology of migraine: a review based on the literature and on personal contributions. *Funct Neurol* 13:7–15
- Nappi G, Costa A, Tassorelli C, Santorelli FM (2000) Migraine as a complex disease: heterogeneity, comorbidity and genotype-phenotype interactions. *Funct Neurol* 15:87–93
- Ambrosini A, Maertens de Noordhout A, Alagona G, Dalpozzo F, Schoenen J (1999) Impairment of neuromuscular transmission in a subgroup of migraine patients. *Neurosci Lett* 276:201–203
- Afrà J (2000) Cortical excitability in migraine. *J Headache Pain* 2:73–81
- Ophoff RA, Terwindt GM, Vergouwe MN et al (1996) Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca⁺⁺ channel gene CACNL1A4. *Cell* 87:543–552
- Afrà J, Cecchini AP, De Pasqua V, Albert A, Schoenen J (1998) Visual evoked potentials during long periods of pattern-reversal stimulation in migraine. *Brain* 121(2):233–241
- Schoenen J (1996) Deficient habituation of evoked cortical potentials in migraine: a link between brain biology, behavior and trigeminovascular activation? *Biomed Pharmacother* 50:71–78
- Maertens de Noordhout A, Timsit-Berthier M, Timsit M, Schoenen J (1987) Effects of beta blockade on contingent negative variation in migraine. *Ann Neurol* 21(1):111–112
- Gerber WD, Schoenen J (1998) Biobehavioral correlates in migraine: the role of hypersensitivity and information-processing dysfunction. *Cephalalgia* 18[Suppl 21]:5–11
- Maertens de Noordhout A, Schoenen J (1999) Transcranial magnetic stimulation in migraine. *Electroencephalogr Clin Neurophysiol [Suppl 51]:260–264*
- Maertens de Noordhout A, Pepin JL, Schoenen J, Delwaide PJ (1992) Percutaneous magnetic stimulation of the motor cortex in migraine. *Electroencephalogr Clin Neurophysiol* 85(2):110–115
- Aurora SK, Cao Y, Bowyer SM, Welch KM (1999) The occipital cortex is hyperexcitable in migraine: experimental evidence. *Headache* 39(7):469–476
- Afrà J, Mascia A, Gerard P, Maertens de Noordhout A, Schoenen J (1998) Interictal cortical excitability in migraine: a study using transcranial magnetic stimulation of motor and visual cortices. *Ann Neurol* 44(2):209–215
- Smith MJ, Keel JC, Greenberg BD, Adams LF, Schmidt PJ, Rubinow DA, Wassermann EM (1999) Menstrual cycle effects on cortical excitability. *Neurology* 53(9):2069–2072
- Montagna P, Cortelli P, Monari L, Pierangeli G, Parchi P, Lodi R, Iotti S, Zaniol P, Lugaresi E, Barbiroli B (1994) 31P-Magnetic resonance spectroscopy in migraine without aura. *Neurology* 44:666–668
- Ramadan NM, Halvorson H, van de Linde A, Levine SR, Helpren JA, Welch KMA (1989) Low brain magnesium in migraine. *Headache* 29:590–593

17. Ferrari MD, Odink J, Bos KD, Malesky MJA, Bruyn GW (1990) Neuroexcitatory plasma amino acids are elevated in migraine. *Neurology* 40:1582–1586
18. Galeotti N, Ghelardini C, Zoppi M, Del Bene E, Raimondi L, Beneforti E, Bartolini A (2001) Hypofunctionality of Gi proteins as aetiopathogenetic mechanism for migraine and cluster headache. *Cephalalgia* 21:38–45
19. Moskowitz MA, Nozaki K, Kraig RP (1993) Neocortical spreading depression of c-fos protein-like immunoreactivity within trigeminal nucleus caudalis via trigeminovascular mechanisms. *J Neurosci* 13:1167–1177
20. Tassorelli C, Joseph SA (1995) Systemic nitroglycerin induces Fos immunoreactivity in brainstem and forebrain structures of the rat. *Brain Res* 682:167–181
21. Sandrini G, Alfonsi E, Ruiz L, Pavesi G, Miceli G, Manzoni GC, Mancina D, Nappi G (1991) Impairment of corneal pain perception in cluster headache. *Pain* 47(3):299–304
22. De Tommaso M, Guido M, Libro G, Sciruicchio V, Puca F (2000) The three responses of the blink reflex in adult and juvenile migraine. *Acta Neurol Belg* 100(2):96–102
23. Sandrini G, Arrigo A, Bono G, Nappi G (1993) The nociceptive flexion reflex as a tool for exploring pain control systems in headache and other pain syndromes. *Cephalalgia* 13:21–27
24. Sandrini G, Martignoni E, Miceli G, Alfonsi E, Sances G, Nappi G (1986) Pain reflexes in the clinical assessment of migraine syndromes. *Funct Neurol* 1:423–429
25. Goadsby PJ, Edvinsson L, Ekman R (1990) Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann Neurol* 28:183–187
26. Moskowitz MA (1991) The visceral organ brain: implications for the pathophysiology of vascular head pain. *Neurology* 41:182–186
27. Wolff HG (1963) *Headache and other head pain*. Oxford University Press, New York
28. Sicuteri F (1976) Hypothesis: migraine, a central biochemical dysnociception. *Headache* 16:145–159
29. Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH (2000) An association between migraine and cutaneous allodynia. *Ann Neurol* 47:614–624
30. Weiller C, May A, Limmroth V, Juptner M, Kaube H, Schayck RV, Coenen HH, Diener HC (1995) Brain stem activation in spontaneous human migraine attacks. *Nat Med* 1:658–660