Is migraine a disorder of the central nervous system?

Alberto E. Panerai

© Springer-Verlag Italia 2013

Abstract The chicken and the egg problem is how, in Italian or in English, some time ago one would have referred to a question as the one to be approached here: “Is migraine a disorder of the central nervous system?” or of the peripheral nervous system? Till some time ago, even an honest basic scientist or clinician could almost equally sustain one or the other origin and find data that substantiate her/his opinion. Nowadays, however, our improved knowledge is pushing in the direction of the central nervous system, although many mechanisms remain unclear. The confusion originates from the important role played by multiple and important bidirectional interactions between the peripheral and the central nervous systems, i.e., the trigeminovascular system and the cerebral cortex. The problems are: Who starts first? Who is not working properly? It appears now that the answer to the question has to be probably searched in the delicate balance present in the central nervous system between excitatory and inhibitory circuits, their adaptation to chronic stimuli and, within these circuits, the balance of neurotransmitters, neuromodulators, transporters and ion channels that keeps them well functioning.

Keywords Migraine · Central nervous system · Inflammation · Neuromodulation

Migraine is probably the consequence of a complex genetic disorder that involves the interplay of multiple genes and

gene–environment interactions. For this reason it appears difficult to follow a common genetic route in order to answer our general question: “Is migraine a disorder of the central nervous system?”

There are good evidences for genetic modifications that determine specific migraine syndromes such as the familiar hemiplegic migraine (FHM) subtypes, but these represent only a small minority of patients. For this reason, I think that using FHM, both as a clinical or experimental model, in order to understand the whole migraine origin is not correct and probably useless. It is a problem comparable to the attempt to understand ALS investigating only those patients or mice that have a genetic superoxydismutase (SOD) genetic modification: ALS is more than that.

The hypothesis that migraine attacks involve the CNS is supported by the observation that they are often preceded, sometime several hours before, by problems with speech, reading, emotional responses and sensory hypersensitivity, and by the observation that also some typical triggers such as stress, hunger, sleep disorders have a central origin. Moreover, it has been shown that patients show CNS abnormal neurophysiological patterns also in the time between attacks.

Peripheral inputs reach the trigeminocervical complex (TCC), that in turn connects to the brain stem (periaqueductal gray, PAG; rostroventromedial medulla, RVM) and structures (hypothalamus and thalamus) that initiate higher connections with the cortex.

The peripheral stimulation at the dura leads to the activation of the primary and secondary somatosensory (S1 and S2) cortices and the insular cortex (pain matrix). The involvement of these projections does also help to understand neurological, cognitive and emotional disturbances that often accompany headache in some patients.

A. E. Panerai (✉)
Dipartimento di Scienze Farmacologiche e Biomolecolari,
Università degli Studi di Milano, Via Balzaretti, 9,
20133 Milan, Italy
e-mail: alberto.panerai@unimi.it

It is very important to remember that TCC also receives descending inhibitory projections that modulate its activity. It comes back here the PAG–RVM circuitry whose stimulation results in inhibition of the trigeminovascular TCC response to dural stimulation; however, we will see that the role of the PAG–RVM circuitry is tricky. Again also the insular cortex comes into play again and sends descending projection to TCC.

Looking at the peripheral hypothesis, this stands mainly on the relation between meningeal and extracranial vasodilatation and the migraine attack. At present, in contrast with its past success, this causative relation seems to be no more tenable or at least not as solid as it appeared. One set of data against the peripheral origin of the disease is the observation that drugs or substances that induce a migraine attack do not always induce vasodilatation, although they are classified as vasodilators, while other drugs or substances induce vasodilatation without triggering an attack. CGRP itself induces a slight vasodilatation that is probably not related to its pain-inducing effect. In order to explain CGRP-induced pain, it has been suggested that this could derive from a role of the peptide in the intraganglionic crosstalk between neurons and glial cells, prompting an inflammatory cascade, that could lead to sensitization throughout the release of proinflammatory cytokines and chemokines that activate TRPV1 or purinergic P2X3 receptors. Moreover, it has to be recalled that the chance that peripheral CGRP can get across the blood–brain barrier in significant amounts remains a problem.

As for other types of pain, inflammation has been suggested to play an important role also in migraine, leading to a neuroinflammation that promotes a sustained sensitization of sensitive afferents whose activity can be maintained independently of the original noxa. This path is common to other pain syndromes and one of its consequences is the development of allodynia, a symptom present also in some migraine patients and that can be blocked by anti-inflammatory drugs and, in experimental models, by anti-cytokine agents. The single steps of this scheme and the whole history of this inflammation remain poorly understood, but pursuing its investigation could prove important in order to develop new therapies. Just to anticipate a possible field of research, let us think of all endogenous mechanisms involved in the resolution of inflammation, that are often started during the acute phase of inflammation, and that could be druggable in order to accelerate the effect; but let us also think that some treatments, although effective in the short time, might negatively affect resolution thus leading to chronicization.

Interestingly, also glyceryl trinitrate infusion can produce inflammation and this, together or not with vasodilatation, could be the real cause of its ability to trigger an attack.

The connection inflammation–resolution–migraine stands in the observation that also migraine attacks resolve spontaneously and this could be linked to the resolution of the underlying inflammation, and some drugs that are effective in the acute attack could favor chronicization (drug overuse?).

It is generally suggested that migraine is triggered by the activity of sensitized trigeminovascular nociceptors that start a pathway toward the brain stem and forebrain, this path, however, seems to be fully active only in migraine patients. It is known, in fact, that CGRP or glyceryl trinitrate trigger an attack only in migraine patients, but not in normal subjects. This observation suggests that normal subjects are able to exert a central control of these inputs that is lacking or imperfect in patients.

As I said, I do not want to approach the genetic problem or use FHM to explain the CNS role in migraine: I would just like to think what might be a general CNS role in migraine. FHMs and related experimental models suggest several possible defects of CNS functioning, e.g., the dysfunction of specific Ca^{2+} channels, Na^+/K^+ ATPase or sodium channels [1], but they cannot be assumed to be common to other types of migraine.

To follow, there are some clues to a primary CNS origin of migraine. A first hint is that migraine headache might arise from a dysfunction of the already quoted PAG–RVM circuitry, leading to incorrect control or a misinterpretation of normal sensory inputs thus perceived as (migraine) pain. Interestingly, migraine attacks imaging studies showed that modifications present during the acute attack are still detectable after its successful therapy, and this is more evident in the PAG–RVM circuitry already quoted above. On this point, it is useful to recollect what was observed in experimental studies, in models of acute pain developing into chronic pain. These studies demonstrated that the activity of this descending pain-inhibitory system, with RVM pain responding “pronociceptive ON” cells and “antinociceptive OFF” cells, switches during persistent stimulation from a pain inhibitory to a pain facilitatory activity. This switch could explain how migraine headache can be generated (maintained) also in the absence of a peripheral sensory input and the generation of allodynia.

A second point for the CNS origin of migraine comes from animal experiments that suggest that cortical spreading depression (CSD), usually related only to the development of aura, might be a direct trigger of migraine. Indeed CSD can induce the release of CGRP from perivascular fibers or might facilitate the release of proinflammatory factors that activate and sensitize meningeal nociceptors. Consistent with the CSD hypothesis, several drugs used in the prophylaxis of migraine with or without aura increase the electrical threshold for CSD induction.

Against a trigger role for CSD is the observation that not all migraine patients experience aura, and that in some patients migraine premonitory symptoms may occur up to 12–24 h before the onset of the aura and headache, meaning that different brain regions are activated well before the onset of CSD.

Another important point in favor of a CNS origin of the disease is that during the pain-free intervals between attacks, one can demonstrate a progressive mounting of symptoms such as stress responses to levels higher than in normal subjects in the same situations, suggesting a dysfunction in central information processing or stress control mechanisms.

It appears that interictal CNS activity might really be the important moment in the disease to look at. As expected, different studies yielded opposite results, suggesting that migraine patients have either hyperexcitable or hypoexcitable stigma, due either to excess of stimulatory inputs/transmission or lack of inhibitory inputs/transmission. As in many neurological diseases, truth has probably to be searched in the middle, i.e., in a not in a dysfunction of the single excitatory or inhibitory system, but in the deranged ability to maintain a (cortical) excitatory/inhibitory balance [1–3].

At this point one can take some tentative, and temporary, conclusions:

- Excitatory or inhibitory balance is probably essential for a correct threshold for response to inputs coming

from the periphery. In this context one has to look at the actors in the CNS modulation game such as serotonin, noradrenaline, acetylcholine, glutamate, GABA and a number of neuropeptides at the different levels from brain stem to cortex [4, 5].

- The big problem, as too often occurs, is the lack of a suitable experimental model or non-invasive techniques for studies in the only real patient, the human.

Conflict of interest I certify that there is no actual or potential conflict of interest in relation to this article.

References

1. Vecchia D, Pietrobon D (2012) Migraine: a disorder of brain excitatory–inhibitory balance? *Trends Neurosci* 35:507–520
2. Pietrobon D (2012) Calcium channels and migraine. *Biochim Biophys Acta*. doi:[10.1016/j.bbamen.2012.11.012](https://doi.org/10.1016/j.bbamen.2012.11.012)
3. Pietrobon D, Moskowitz MA (2013) Pathophysiology of migraine. *Ann Rev Physiol* 75:365–391
4. D’Andrea G, D’Arrigo A, Delle Carbonare M, Leon A (2012) Pathogenesis of migraine: role of neuromodulators. *Headache* 52:1155–1163
5. Leone M, Sacerdote P, D’Amico D, Panerai AE, Bussone G (1992) beta-Endorphin concentrations in the peripheral blood mononuclear cells of migraine and tension-type headache patients. *Cephalalgia* 12:155–157