Medical Hypotheses 74 (2010) 750–753

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

How triggers trigger acute migraine attacks: A hypothesis

Ambar Chakravarty *

Department of Neurology, Vivekananda Institute of Medical Science, 1E 1202, Avishikta II, Calcutta 700 078, India

ARTICLE INFO

Article history:
Received 11 October 2009
Accepted 14 October 2009

SUMMARY

A trigger is an integral part of any acute migraine attack. In this article, the author argues that triggers, identifiable or not, must be present in all attacks of migraine headache. It is hypothesized that triggers, internal or external, induce the onset of cortical spreading depression (CSD) in a pre-existing hyper-excitable cortex of a migraine brain, initiating the process of pain generation. The author hypothesizes on a second site of action of triggers at the level of trigeminal nuclear complex (TNC) in brain stem, the cell station of second order neuron pathway for migraine pain transmission to the sensory cortex. The author suggests existence of a hypothetical 'gate' at TNC level where incoming trigeminal migraine pain impulses would 'compete' with descending inhibitory signals from brain stem pain modulatory neurons, to get entry into the central nervous system. The author draws analogy with the 'gate control' mechanism operative at the dorsal horn level for spinally transmitted somatic and visceral pain. It is suggested that the hypothetical 'gate' at TNC level is controlled by activity of 5HT receptors, thus supporting the concept of an additional site of action of triptans in aborting acute migraine pain. The suggested hypothesis on mechanism of action of triggers, offers theoretical basis for efficacy of currently available pharmacologic and non-pharmacologic therapies for abortive and prophylactic treatment of migraine.

In a recently published article in this Journal [1], we had briefly but critically evaluated the current thoughts on the pathophysiology of migraine and introduced an all embracing concept to clear the confusion arising out of two divergent views on migraine pain generation sites – peripheral (dura and vessel wall) versus central (brain stem). On the basis of our understanding of migraine pathophysiology, we proposed a unifying concept which would bring migraine at par with other pain syndromes like neuropathic or nociceptive pain. In the course of this article [1] we commented that in migraine, a structurally normal nervous system reacts abnormally to apparently non-noxious stimuli resulting in pain perception. To hypothetically decipher how an apparently non-noxious stimulus behaves like a noxious one (that is it becomes a trigger) would be the prime objective of this article. Recently Lambert and Zagami [2] hypothesized on the possible mechanism of action of migraine triggers. In the present article, I wish to present a modified conceptual model on mechanism of triggering which would be more consistent with the structural organization of migraine pain pathway discussed earlier [1] as also with migraine therapeutics – both abortive and prophylactic.

Highlights on migraine pathophysiology

There is perhaps not much hesitation now to accept that migraine is essentially a cerebral disorder. In our previous publication [1] we compared the migraine pain circuitry to that of a complex electrical circuit with a power source at one end and an electrical bulb at the other with several regulators and switches on the way.

We have agreed with the arguments of Olesen et al. [3] that pain generation in migraine is peripheral rather than central and the initiating event is a curious cortical electrochemical phenomenon called cortical spreading depression (CSD) which due to liberation of noxious chemicals stimulates the afferent trigeminal nerve endings innervating the overlying meninges and blood vessels. Takano et al. [4] have suggested that migraine pain can arise from CSD because of the hypoxia, edema and inflammation that CSD can produce. Once generated, transmission of pain occurs through a three neuron pathway and involve three levels of structurally and functionally organized systems (first peripheral sensitization at trigeminal ganglionic level; second central sensitization at various brain stem nuclei namely trigeminal nuclear complex, (TNC) rostral ventral medulla (RVM), locus coeruleus (LC) and periaqueductal grey (PAG) and lastly the thalamus) for pain perception at the sensory cortical matrix. All the brain stem nuclei modulate pain in its onward journey to the cortex. The organization is very similar to what had been proposed in connection with appreciation of neuropathic and nociceptive pain syndromes [1]. So, what is special about migraine?

In their book, Lance and Goadsby [5] commented "migraine may be regarded as a hereditary tendency to have headache characterized by associated signature symptoms such as nausea or sensitivity to light. The basis of this predisposition is instability in control of pain coming from the intracranial structures and sensitivity to changes in the central nervous system".

* Tel.: +91 33 24843283.
E-mail address: saschakra@yahoo.com

0306-9877/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.mehy.2009.10.027

This statement very subtly hints at the concept of a migraine brain which is not new. What it means essentially in physiological terms, is that the cortices of migraineurs are hyper-excitable or under-inhibited. Such a hyper-excitable cortex is a fertile soil for development of aberrant cortical discharges which are the very first event in the phenomenon of CSD. There is adequate literature evidence and support for this contention [6–12]. This concept of a hyper-excitable cortex with occasional aberrant cortical discharges in migraine, brings migraine and epilepsy closer – a concept which is over a century old. We shall examine the therapeutic implication later. This hyper excitability (as in epilepsy) in migraine is certainly genetically determined and at least two genes have been described [13–15] in relation to familial and sporadic hemiplegic migraine. These genes are essentially involved with calcium channels and with actions on the NA^+–K^+–ATPase systems. This would suggest the role of these in the generation of CSD.

So what triggers do? In subjects with a low 'migraine threshold' having a hyper-excitable cortex, a trigger precipitates aberrant cortical discharges which give way to CSD – the initiator of migraine pain. It would not be appropriate to consider CSD as a trigger; CSD is the initiator which is 'trigged' to happen by the triggers in genetically susceptive subjects. This is how an apparently non-noxious stimulus behaves like a noxious stimulus in a migraine prone subject. This is my first proposition regarding mechanism of action of triggers – that they precipitate CSD, in migraine susceptible subjects but not in others. My second proposition in this connection is that all migraine attacks are initiated by CSD. This may be a little difficult to prove. Attacks of migraine with aura (in any form) are certainly initiated by CSD where CSD produces a focal neurological phenomenon which manifests as an aura. But does CSD occur during attacks of migraine without aura? The issue is not yet resolved. Although there is some suggestion that CSD also occurs during migraine without aura, the evidence is not robust. However, subjects having attacks of migraine with aura, also get attacks without aura. Hence, there can be no reason to suspect that different pathogenetic mechanisms are operative at different times in the same individual. Whether an aura would develop or not, depends upon the particular brain area affected by the process of CSD. It is often said that during attacks of migraine without aura, the so called 'silent areas' of the brain are affected by CSD. This may be true but experimental or clinical investigative evidences are lacking. Furthermore whether an aura would occur or not is certainly genetically determined. In Western population, the reported incidence of subjects with migraine with aura is around 30%. However, in our experience in India, both among children and adults, subjects with migraine with aura constitute only about 3% of subjects studied in two large samples [16,17]. On the whole therefore, it appears that all migraine attacks must have CSD for pain initiation through robust evidence is lacking at the present time.

Triggers of migraine attacks

From what had been discussed in the previous section, it would be reasonable to hypothesize at this stage that all migraine attacks need to be triggered. The trigger is the stimulus to generate the CSD in an already hyper-excitable cortex. In general, it is said that about 25–50% subjects can associate their migraine attacks with some specific trigger. Our observations have been different. In a recently published study, in 200 consecutive children with migraine, one or more triggers could be detected in 94% of children when studied retrospectively (with a help of a questionnaire which included a long list of possible triggers) and 100% of them when studied prospectively for 6 months with the help of headache diaries and using the same questionnaire [18]. A similar study done retrospectively enrolling 800 consecutive adult subjects with migraine (yet unpublished) yielded similar results. Comparable data was generated in a study of adult migraineurs by Kelman [19]. Also Lambert and Zagami [2] mentioned that triggers can be identified in most migraineurs. Our study [18] can be criticized on the ground that a 100% occurrence would go against the concept of Null hypothesis [20]. I would argue that triggering of migraine attacks is a universal phenomenon and hence the Null hypothesis may not be applicable. I believe, detection of triggers in a group of subjects is dependent on the zeal with which they are searched for. However, still, even in our study [18], many subjects could not identify a trigger precipitating some of their attacks. There can be several reasons. And yet unidentified trigger may have occurred or the trigger had been of so short in duration, which the subject failed to notice it. What is important is to note that often several possible triggers are implicated and then it is impossible to determine which one or ones actually triggered the CSD. This is particularly true for environmental triggers and in a country like India, bright sunlight, heat, humidity, atmospheric pollution, all occur simultaneously. Environmental triggers are often constant for a particular season. Then why would a person develop headaches on some days but not in all? It is likely, this is related to the variation in the intensities of the stimuli. Triggering has to be a very specific phenomenon. These however, have not been worked out in detail.

How do triggers initiate CSD?

Triggering is essentially a cortical phenomenon. Triggers, in general may be viewed as sensations (perceptible or non-perceptible) and hence need to be appreciated at cortical level. Triggers may travel to cortex spinally using conventional sensory pathways (e.g. heat, head bath), may use special sensory pathways (light, sound, smell) or humorally through blood stream (sex hormones, chemicals derived from food items). Reaching cortex, these would, in susceptible subjects, may act by altering ionic flow across cell membranes by modifying the activity of Ca^{++} channels or through Na^+–K^+–ATPase systems. This would induce CSD in an already hyper-excitable cortex. Psychic triggers like stress, anxiety and depression are essentially cortical in origin and are mediated through activity of neurotransmitters. Fasting is probably a hypothalamus generated trigger. There is hardly any experimental proof for this concept but it bears a close analogy to how epileptic discharges arise in genetically predetermined individuals. Epileptic seizures are often precipitated (e.g. by lack of sleep, photic stimulation, stress and anxiety).

This concept of migraine pain generation by CSD in a hyper-excitable cortex being triggered by identifiable or non-identifiable triggers and the close similarity with the concept of epileptic seizure generation, forms the theoretical basis of use of anti-epileptic drugs (valproate, topiramate and gabapentin) in migraine prophylaxis. These agents tend to reduce the hyper-excitable state of the cortex thereby preventing development of CSD, induced by triggers.

One thing needs to be appreciated at this stage. Triggers are all appreciated at cortex (consciously or unconsciously), but the information are most likely projected downstream through descending pathways to the brain stem nuclei which include the migraine pain modulating nuclei like PAG, LC and RVM.

Triggers and brain stem functions

Lambert and Zagami [2] hypothesized that 'most migraines have triggers that produce excitation of cortical neurons and that this excitation directly inhibits neurons in two brainstem nuclei: the periaqueductal grey matter (PAG) and the nucleus raphe magnus (NRM). These nuclei then release their ongoing descending control