Migraine, cortical excitability and evoked potentials: a clinico-pharmacological perspective

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Coppola et al., (2005) studied somatosensory evoked high-frequency oscillations (HFO) in migraine patients between attacks and advances the hypothesis that the habituation deficit in migraine patients is owing to a reduced pre-activation level of sensory cortices. While further proposing that a reduced interictal excitation ('pre-activation') level might be the pathophysiological basis of migraine attacks, these authors acknowledge that contradictory laboratory evidence for both increased and decreased cortical excitability as well as decreased and normal function of inhibitory cortical interneurons have been presented by other investigators through study of transcranial magnetic stimulation and psychophysical studies. Additionally, the paucity of definitive knowledge about neural generators involved in HFOs is underscored.

It is essential to maintain a clear conceptual distinction regarding the state of the brain physiology between the headache and the headache-free states in migraine. Hypersensitivity to light or noise is a migraine attack-related phenomenon; nevertheless, such hypersensitivity cannot be used to support the concept of cerebral cortex hyperexcitability between attacks. Second, a critical limitation of this study (Coppola et al., 2005) is the decision to select a period of 72 h (3 days) as the cut-off interval separating ictal periods (headache phase) from inter-ictal (in-between headache attacks) periods. It has been assumed that an interval of 72 h before or after a migraine attack is sufficient to place the patient in the basal, unstrressed and non-aroused state. In patients with frequent migraine attacks, say 1 or more every week, such an assumption does not necessarily hold true. The prodrome of migraine can last several hours to a few days (Peatfield, 1988). Moreover, migraine attacks (with or without aura) are associated with substantial increases in plasma methionine-enkephalin, which return to baseline only slowly in the pain-free period (Mosnaim et al., 1989). Also, migraine-attack related inconsistently-lateralized prolonged cranial vasodilatation persists for 48 h after cessation of headache, subsiding gradually to normal levels by 6 days (Kobari et al., 1989). Finally, since evoked potentials in migraine basically study the state of stress-associated arousal accompanying perceptions of challenge, threat, harm/loss, and coping options—primary and secondary appraisals (Schwarzer, 1998)—and stress below the threshold of headache is distinctly possible in migraine patients (Passchier, 1994), it is useful to consider the operation of a continuum of stress-associated evoked responses. Being based on entirely subjective perception, arousal responses vary from patient to patient and in the same patient on different occasions; reproducibility of evoked responses in the same or different cohort is likely to be limited. Nevertheless, more often than not the early phases of arousal in migraine patients keep both the aura as well as the headache at bay; post-stress headache is a characteristic feature of migraine (Gupta, 2004a; website URL: http://www.biomedcentral.com/1471-2377/4/17/comments#106454) and responses early in the arousal continuum, regardless of the source of generation, are probably adaptive in nature possibly reflecting a learned conservation of neuronal functional ‘potential’ or ‘energy’ for a more demanding challenge that generally follows subsequently. Maintaining a broader perspective, it is difficult to conceive how a consideration of reduced thalamo-cortical excitation or demonstration of other putatively more precise neuronal generators can overcome the critical limitations of the neuronal theory of migraine (Gupta, 2005).

Migraine pathophysiology is a rather loose network of several assumptions. Nevertheless, certain pharmacological...
facets offer clear signposts in the evolution of this poorly-understood entity. We have to contend with evidences indicating that drugs such as atenolol, which do not freely cross the intact blood-brain barrier (BBB), currently are included in the list of first-line prophylactic agents, thereby raising issues with a central role for brain neuronal origin of migraine (Gupta, 2004b). Migraine prophylactic agents unambiguously affect the primary pathogenetic processes in migraine (afferent limb) and are not expected to have any influence on the events of the trigeminovascular system (efferent limb of migraine). Propranolol, by virtue of brain noradrenergic blockade, cannot be expected to improve reduced thalamo-cortical excitation to which Coppola et al., (2005) have attributed a central pathogenetic role. If propranolol ‘worsens’ dampening of thalamo-cortical excitation but prevents migraine, logically the latter is a biologically beneficial physiological adaptation. It is also incorrect, as it has been assumed (Coppola et al., 2005) that all migraine prophylactic agents depress cortical (hyper)excitability. Amitriptyline, an established combined activator of both noradrenergic and serotonergic brain neuronal systems, is one of the most widely used migraine prophylactic agents. If both brain noradrenergic suppression (induced by propranolol) and excitation (induced by amitriptyline) can prevent migraine, a reorganization of concepts is essential. Moreover, the combination of propranolol and amitriptyline that has been found to be therapeutically useful for migraine or mixed headaches (Mathew, 1981) appears to be pharmacologically invalid insofar as alteration of brain noradrenergic function is concerned but is nevertheless clinically effective, and, therefore, conceptually challenging. Third, drugs that abort the aura of migraine, such as nifedipine, nitrates and isoproterenol, do not significantly cross the BBB and, therefore, cannot influence the visual cortex. Fourth, peripheral frontotemporal application of nitroglycerine can precipitate ipsilateral headache (BONUSO et al., 1989). We have to begin to question the long-held view that the brain/brainstem is indeed the primary and exclusive source of genesis of migraine headaches.

The study of evoked potentials in migraine constitutes an interesting physiological phenomenon that cannot, however, be integrated into a defensible overarching theory of migraine or provide fresh impetus to create the much-needed research vision for migraine.

References