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Review

From different neurophysiological methods to conflicting pathophysiological views in migraine: A critical review of literature

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HIGHLIGHTS

- An impressive amount of studies has been conducted, with inconsistent results, to non-invasively investigate the cortical excitability state in migraine.
- Various methods of testing brain excitability, as they induce different degrees of cortical activation, could shed light on different aspects of the so-called migraine cortical "dysexcitability".
- Different pathophysiological mechanisms might coexist in migraine, possibly being either expression of increased cortical responsivity or compensatory mechanisms seeking to stabilize the cortical excitability level.

ABSTRACT

Abnormal increased cortical responsivity to various types of stimuli plays a major role in migraine pathogenesis. Neurophysiological studies, however, have provided ambiguous findings of either hypo or hyper cortical excitability. This is why the term "dysexcitability" has been recently proposed to indicate a more general dysregulation of cortical excitability. The aims of this review are: (1) to provide existing knowledge and research advances in migraine pathophysiology; (2) to propose a unitary interpretation of apparently conflicting neurophysiological findings.

Data of studies conducted in migraine through various evoked potentials techniques and non-invasive brain stimulation methods are reviewed, and in some cases reinterpreted according to more recent findings on migraine pathophysiology. In particular, we emphasize the concept that various methods of testing brain excitability may induce different degrees of cortical activation depending on the stimulus parameters used (e.g., intensity, frequency, and duration of stimulation), so shedding light on different pathophysiological aspects.

Finally, we try to reconcile apparently conflicting neurophysiological data in the light of a unitary pathophysiological model, suggesting that a condition of interictal cortical hyperresponsivity, possibly due to a glutamatergic dysfunction, could represent the primum movens of migraine pathogenesis.

Contents

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1. Introduction

To date, it is widely accepted that susceptibility to the migraine attack mainly relies on dysfunctional mechanisms that regulate the cortical excitability level, i.e. the way in which the brain reacts to a large number of exogenous and endogenous stimuli. In migraine, the excitability of different cortical areas has been extensively investigated using evoked potentials (EPs) techniques and non-invasive brain stimulation methods such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Considering the enormous amount of data collected over the last decades, it is not our intention to do a complete revision of the literature. For a more detailed description, please refer to other reviews focused on specific aspects of migraine pathophysiology, such as that by Brigo et al. (2012) on visual cortex excitability, Coppola et al. (2009) on cortical habituation, and Brighina et al. (2009) on intracortical inhibition.

This review arises as an attempt to summarize and possibly reconcile previous conflicting neurophysiological findings in migraine (Table 1). Our hypothesis is that the migraine cortex can appear either hyperexcitable or hypoexcitable depending on the stimulation procedures used to test brain excitability. Thus we will try to show that opposite neurophysiological results, that have lead to the concept of cortical "dysexcitability" in migraine (Valeriani and Le Pera, 2007), might reflect different neural responses to various brain stimulation methods. In particular, we will focus on studies showing that the migraine cortex differently reacts to the same stimulation paradigm as a function of the different test parameters used (e.g., intensity, duration, and frequency of stimulation). Indeed, this important finding suggests that after induction of different magnitudes of cortical activation, different pathophysiological aspects could be revealed.

In the following paragraphs, we will discuss the main findings taken in support of current hypotheses of migraine pathogenesis, trying also to provide a unitary pathophysiological model.

2. Does the migraine attack start at the cortical level?

Migraine headache represents one of the most frequent pain disorders, affecting millions of people of all ages worldwide (Stovner et al., 2007). In agreement with the trigeminovascular theory, first proposed by Moskowitz et al. (1989), the headache is due to activation of the perivascular trigeminal fibers that convey pain signals centrally via the brainstem (Olesen et al., 2009). However, it still remains to be elucidated through which mechanisms a large number of factors triggering the attack activates the trigeminovascular system. Several lines of evidence support the idea that the onset of a migraine attack takes place in the cortex: (1) prodromal symptoms such as irritability, photophobia, phonophobia, and osmophobia, indicate that a generalized increase in cortical responsivity may precede the headache (Rossi et al., 2005; Andreatta et al., 2012), (2) various factors affecting cortical excitability modulate the threshold for triggering the attack (e.g., menstrual cycle and sleep–wake cycle) (Welch, 2003), (3) cortical spreading depression (CSD) waves, that represent the pathophysiological substrate of migraine aura, can activate the trigeminovascular system (Bolay, 2012), (4) neurophysiological findings show that significant changes in the cortical excitability level precede the headache onset (Sand et al., 2008; Siniatchkin et al., 2009; Cosentino et al., 2014b). However, the precise pathogenetic mechanisms by which changes in cortical excitability could activate the trigeminovascular system, as well as the pathogenetic role played by subcortical structures such as brainstem, thalamus, and hypothalamus, which are bidirectionally connected with the cerebral cortex, remain to be elucidated. Experimental animal models of CSD show that various vasoactive and nociceptive substances released from brain parenchyma during CSD, spreading through the extracellular compartment, could reach and activate the perivascular trigeminal fibers (Bolay et al., 2002; Bolay, 2012; Obrenovitch et al., 2002). Such a mechanism primarily refers to the migraine with aura (MwA) attacks. Indeed, although there is some suggestion that CSD could also occur during migraine without aura (MwoA) attacks, mainly affecting the so-called "silent areas" of the brain, strong evidence is lacking in this regard (Chakravarty, 2010). Notwithstanding, it could be suggested that in MwoA, even without assuming the existence of silent CSD waves, several stimuli acting on a hyperresponsive cerebral cortex could induce an over-activation of several brain areas, which in turn could determine metabolic parenchymal changes triggering the attack (Bolay, 2012). In addition, other possible pathogenetic mechanisms of migraine pain include abnormal modulation of the trigeminovascular afferents through cortico-trigeminal pathways (Noseda et al., 2010; Noseda and Burstein, 2013).

3. What is the origin of the abnormal cortical excitability state in migraine?

Migraine is associated to an increased responsiveness of the brain to any kind of environmental stimuli. Hyperresponsivity is detectable not only during the attack, but also in the pain-free period. Migraine patients are more sensitive to light and sound with respect to healthy people (Main et al., 1997). The threshold for visual- and auditory-induced discomfort is reduced in migraineurs, and it further decreases during the attacks (Vingen et al., 1998; Woodhouse and Drummond, 1993). Interictal high cortical excitability goes beyond the sensory cortices, being also detectable in motor cortical areas (Brighina et al., 2005; Cosentino et al., 2011; Siniatchkin et al., 2007) and in brain structures involved in the processing of emotional (Andreatta et al., 2012) and cognitive information (Kropp and Gerber, 1995).

The understanding of the pathophysiological mechanisms underlying migraine cortical hyperresponsivity has been proven to be a significant challenge for researchers. Some authors have found evidence of reduced cortical preactivation by subcortical brain structures (Coppola et al., 2007a, 2009). Others have claimed increased cortical excitability due to a glutamatergic dysfunction (Aurora et al., 1998; Brighina et al., 2011; Siniatchkin et al., 2012), or to an impairment of the intracortical inhibitory activity (Aurora et al., 1999; Chadaide et al., 2007; Curra et al., 2007; Mulleners et al., 2001; Valeriani et al., 2005). As discussed below,