DEBATE: DOES THE FIRST PHASE OF A MIGRAINE ATTACK ORIGINATE IN THE CEREBRAL CORTEX OR THE BRAINSTEM?

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Migraine affects a large segment of the human population, implicating mechanisms and pathways essential to the organization of the human brain. Migraine aura, the prodrome phase of migraine with aura, is originating within the occipital cortex and it is linked to the cortical spreading depression (CSD). CSD is a slowly propagating depolarization of neurons and glia cells that has been recorded within the hippocampus, striatum, and cerebellum as well as cortex. CSD is characterized by regional blood flow changes within the occipital cortex in migraineurs during spontaneous visual aura (Hadjikhani et al., 2001). Some migraineurs however, exhibit blood flow changes similar to CSD and aura but are subjectively unaware that the phenomenon is propagating in. This so-called “silent” aura may be more common than previously appreciated and may explain why many patients experience migraine headaches both with and without aura. Experimental evidence supports a relationship between CSD and trigeminal activation, triggered either by perivascular ion (Bolay et al., 2002), or neuropetide changes (NO and CGRP in particular, Armstrong et al., 2009; Wahl et al., 1994) that have been recorded during CSD propagation within the cortex. Susceptibility to CSD and to migraine appears to be genetically determined (de Vries et al., 2009). In some migraine subtypes, genes controlling translocation of calcium, sodium and potassium have been implicated, altering the susceptibility to CSD together with female reproductive steroids (Dalkara et al., 2006; Finocchi & Ferrari, 2011). More recently it has been shown that KCL induced CSD in rats activated trigeminal neurons within laminae I and II of brainstem, further indicating that CSD constitutes a nociceptive stimulus capable of activating peripheral and central trigeminovascular neurons that underlie the headache of migraine with aura (Zhang et al., 2011). At least for a subgroup of migraineurs consequently, for those they are suffering from migraine with aura and also experience migraine attacks without aura, CSD seems to be among the first events. What about those that are suffering exclusively from migraine without aura and never experience migraine auras? What fascinates those who study migraine is that the brain is essential to both triggering an attack and processing it, via multifaceted networks, neurotransmitters, and receptors. Multiple triggers have been implicated so far, by using advanced neuro-imaging techniques, including brainstem and midbrain structures mainly (Weiller et al., 1995; Danuelle et al., 1997). For those patients they never experience auras, the migraine generator may be located within subcortical places therefore. What remains common in all migraineurs is the gene induced brain hyperexcitability (Welch, 2003; Chen et al., 2011) that makes the brain “nervous”, ready to hyper-respond (Copolla et al., 2007) in any environmental or hormonal or neurotransmitter change by activating specific networks either cortical or subcortical leading to migraine headache with, or without aura, respectively. Hence, there is no longer any need to debate whether CSD occurs within human brain or to doubt its importance as a premier event in migraine pathophysiology (Moskowitz, 2006).