DOES THE FIRST PHASE OF A MIGRAINE ATTACK RESIDE IN THE CORTEX?

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Migraine attack is generated by the complex interaction of various players such as genetic predisposition, environmental and intrinsic factors. However in quest of the origin of a migraine attack is challenging task and the scientific evidences so far indicate the contribution of cerebral cortex and particularly cortical spreading depression (CSD), as the most likely initiating event. In my talk I will provide research data that demonstrates the cortical involvement in migraine headache.

Migraine aura originates clearly from cerebral cortex (Hadjikhani et al, 2000). CSD, a pathophysiological event underlying aura is confined to the cerebral cortex, leading to various neuronal and vascular changes in brain parenchyma as well as in the meningeal membranes called pia, arachnoid and dura mater (Bolay & Moskowitz 2005). CSD is also able to induce trigeminovascular activation and neurogenic edema that is a characteristic feature of headache phase (Bolay et al, 2002). Imaging techniques demonstrated the altered activation of occipital cortex at the beginning of an attack regardless of aura (Cao et al, 1999).

Recent genetic and pharmacological findings are also supportive of important role of CSD in migraine. Otosomal dominantly inherited form hemiplegic migraine is caused by mutation of ion channels or transporters such as CACNA1A and SCNA1 or Na+-K+ ATPase, in a way that results in release of excessive glutamate from neurons, reduced uptake of glutamate from the synaptic cleft into glia, and/or reduced buffering capacity to potassium ions. The common result of all three identified mutations is the hyperexcitability and reduced threshold for CSD induction, which all probably contribute to the vulnerability of the brain to migraine attacks. From the therapeutic perspective, the efficacy of certain anti-epileptic drugs in migraine patients and their action on excitability or even on CSD is noteworthy.

Electrophysiological and clinical studies are essentially in favor of cortical dysfunction and disclose increased response of migraineur brain to various external stimuli that is compatible with cortical hyperexcitability or hyperresponsivity (Coppola et al, 2007). In that sense the demonstration of hyperexcitability and sustained increase in the efficacy of synaptic transmission in the affected neocortex as a longterm complication of CSD in human brain tissue is remarkable. Impaired neurovascular coupling associated with CSD was reported. CSD in lissencephalic brain was demonstrated to induce significant redox state in the cerebral tissue that was improved by increased O2 supply. CSD per se was shown to induce insufficient glucose supply for as long as 30 minutes in gyrencephalic brain. Emerging of CSD probably induce a vicious circle where longterm enhanced synaptic efficacy and increased excitability renders the cortical tissue for the next CSD , particularly in the setting of metabolic compromise such as hypoxia and decreased glucose supply. Osmophobia in migraine is worth of mentioning since the perception of scent does not require any subcortical connection. Osmophobia seems to be specific to migraine (Zanchin et al, 2007) and obviously associated with cortical excitability change.

Despite clear demonstration of cortical participation in migraine, the contribution of other brain structures including subcortical nuclei to headache generation and the sequence of neurobiological events leading to an attack remain unclear.