

Cortical spreading depression is NOT the inducer of all migraine attacks.

Lars Edvinsson, Dept of Medicine, Lund University, Sweden

Migraine is a complex disease surrounded by numerous hypotheses. No doubt there is a genetic background but only mechanistically shown for hemiplegic migraine with glutamate as a common trait: hyperexcitability and reduced threshold for induction. It is a challenge to investigate the early phase of migraine attacks for technical reasons. Olesen (1981) early described rCBF alterations following injection of the radioactive tracer $^{133}\text{Xenon}$ and later confirmed by MRI (Hadjikhani 2001); there was first an initial hyperemia followed by oligemia that spread across the cortex anteriorly without respecting the vascular territories. In addition there was close correlation between rCBF changes and the observed neurology. Woods (1994) reported in a PET study bilateral spreading wave of cerebral hypoperfusion in spontaneous migraine attack, associated by headache but without clear aura. Hadjikhani described a spreading wave of rCBF reductions with MRI in one patient that induced a migraine aura during basketball training. The symptoms observed in these studies correlated with the neurology symptoms. Thus, evidence exists for association between the aura phase preceding pain in a migraine attack and association with reduction in rCBF.

Numerous experimental studies have examined induced cortical spreading wave of depression (CSD) as a surrogate method to obtain and understand this early part of a migraine attack but only scant clinical data exist. CSD leads to dramatic alterations in cerebral hemodynamics, however, mechanisms involved in promoting and counteracting cerebral vasodilator responses are unclear (Busija 2008). Experimental data suggest that the hyperemia phase as seen in rodents does not appear in primates but the cortical depression can be induced (Lauritzen).

Is the cortex involved in all migraine attacks and a starting point?

Maniyar (2014/5) recently revealed subcortical activation in the premonitory phase (posterolateral hypothalamus, midbrain tegmental area, periaqueductal grey, dorsal pons) and in various cortical areas including occipital, temporal and prefrontal cortex in conjunction with glyceryl trinitrate-triggered migraine attacks. These brain activations can explain many

of the premonitory symptoms. Despite demonstration of cortical participation in migraine aura, the contribution of other brain structures including subcortical nuclei may indicate that the aura phenomenon is present only in some patients; the sequence of neurobiological events during a migraine attack remains to be elucidated further.