CORTICAL SPREADING DEPRESSION IS NOT INDUCER OF MIGRAINE ATTACKS IN GENERAL

Lars Edvinsson
Sweden

Migraine is a complex disease surrounded by numerous hypotheses. No doubt there is a genetic background but only clearly 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 early described rCBF alterations following injection of the radioactive tracer ^{133}Xenon; there was close correlation between rCBF changes and the observed neurology. Woods 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 correlated with the observed neurology. Thus, evidence exists for association between the aura phase preceding pain in a migraine attack and associates 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 however scant clinical data exist.

Is the cortex critical for the pathophysiology of a migraine attack?
The CSD is a phenomenon confined to the cerebral cortex. In experimental studies CSD can be induced by pricking the cortex with a needle or by local administration of high potassium or by other agents. This results in a localized change in neuronal and vascular activations that affect both the cortex neurons and the cortical blood vessels leading to changes in brain parenchyma blood flow. Wahl observed that the hyperaemic phase was in part dependent on CGRP but not the depression. Bari found that the hyperaemic phase was reduced in capsaicin treated animals. McCulloch showed that CGRP is a strong cerebral arteriolar vasodilator originating in trigeminal nerves which release CGRP after activation and involved in a reflex designed to prevent induced vasoconstriction that could jeopardize the brain circulation.

Is CGRP released in conjunction with CSD?
There exist CSD studied which suggest activation of the trigeminovascular pathway. Ebersberger reported that neither single CSD nor a series of CSD alter ongoing neuronal activity or mechanical or thermal sensitivity of the deeply located neurons to stimulation of their receptive fields on the dura mater. The direct measurements by Piper addressed the CGRP issue in cat; he found no increase in CGRP following CSD. Direct stimulation of the trigeminal ganglion elicits CGRP release in cat and man (Goadsby). This only suggests that CGRP is not the initiator of a migraine attack but is released during the pain phase of the migraine attack. Thus, Goadsby showed no obvious difference in the CGRP release between genuine attacks of migraine with or without aura.

Is the cortex involved in migraine attacks?
Maniyar 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.