

## **Debate: Migraine starts in the cortex**

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A cerebral cortical phenomenon known as cortical spreading depression (CSD) was linked to lateralized headache and shown to be able to activate peripheral trigeminal fibers and second order trigeminal neurons in the brainstem nucleus (TNC). CSD is implicated in releasing CGRP and nitric oxide from trigeminal nerve endings and leading to neurogenic inflammation in the dura mater. CSD is a key to understand familial hemiplegic migraine phenotype, critical involvement of glutamatergic synapse, female hormonal influence and the efficacy of preventive anti-migraine drugs.

Animal studies investigating the mechanisms of migraine and CSD are commonly conducted under anesthesia, despite the fact that pain is a conscious experience. Anesthesia have profound effects on the mechanisms by which CSD is initiated and propagated, and clearly prevents observation of any associated behavioral response. Functional decortication of one hemisphere by CSD in lissencephalic brain would result in transient visual, somato-sensory & motor deficits. CSD in freely moving lissencephalic animals evoked reduced locomotor activity, freezing & grooming episodes and emitted pain calls (22-27 KHz) during freezing episodes. Activation of thalamic reticular nucleus was detected by CSD in only awake animals. Electrocorticographic recordings demonstrated the direct propagation of CSD waves in to thalamic reticular nucleus. Activation was unilateral and lateralized to the side that CSD occurred. It was also lateralized to the side that trigeminal pain nucleus is activated. It was dependent on full conscious experience as highly vulnerable to anesthetics. Blockade of TRN activation by valproate, triptans and CGRP antagonists implicated its relation to nociception. CSD selectively activated visual sector of TRN, though other six TRN sectors of auditory, gustatory, visceral, somatosensory, motor and limbic TRN were not affected by CSD.

TRN consists of GABAergic neurons that surround the thalamus. TRN projects to thalamic relay nuclei in an inhibitory manner and receives glutamatergic excitatory afferents from both cortex and thalamic relay nuclei. TRN mainly functions as a gatekeeper of sensory outflow to the cortex, which is involved in selective attention, lateral inhibition, and discrimination of sensory stimuli. Burst firing of TRN neurons inhibits thalamo-cortical transmission and are associated with sleep spindles or silent periods during wakefulness. Lack of bilateral activation in TRN is against non-specific attention or being awake. Thalamic burst firing occurs spontaneously in human neuropathic pain conditions and also following noxious stimulation. Fifty to 65% of neurons in somatosensory TRN are nociceptive. Cav3.1 & 3.2 (T-channel) knockout mice, exhibit increased threshold for somatic & visceral nociception, which are incapable of thalamic burst firing, and fewer bursts. Oscillations in the low-frequency spindle range observed during freezing periods following CSD is suggested to be associated with pain perception.

Involvement of TRN as a subcortical thalamic structure by a cortical event is important to explain several clinical features of migraine such as 1) Dysfunction of the GABAergic neurons in TRN would result in enhanced transmission of sensory information to the visual cortex, 2) Photophobia and

visual hallucinations of aura may reflect dysregulation of visual stimuli by the TRN, 3) TRN could play a role in either termination or initiation of an attack as sleep is closely related with migraine, attacks are often associated with the circadian cycle and are typically relieved by sleep, 4) an activation of an ipsilateral central route particularly in awake subjects could play also a role in activating ipsilateral brainstem pain structures secondary to cortical activation.