Migraine mice exhibit enhanced excitatory transmission at cortical synapses

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New research is unraveling the complex brain mechanisms associated with disabling migraine headaches. The study, published by Cell Press in the March 12th issue of the journal *Neuron*, reveals that perturbation of the delicate balance between excitation and inhibition may make the brain more vulnerable to migraine attacks.

The brain mechanisms that cause debilitating migraine headaches are not well understood. However, previous neuroimaging studies have suggested that the visual disturbance known as migraine aura is due to a phenomenon called cortical spreading depression (CSD). CSD is a wave of strong neuronal depolarization that slowly progresses across the cerebral cortex, generating a transient increase in electrical signals followed by a long-lasting neural suppression. It has also been suggested that CSD may trigger mechanisms that initiate the migraine headache.

Familial hemiplegic migraine (FHM) is a subtype of severe migraine with aura. Interestingly, recent animal studies have shown that mice carrying the mutation (FHM1) that causes human FHM are more susceptible to CSD. "Investigation of the cortical mechanisms that produce facilitation of CSD in the FHM mouse models may provide unique insights into the unknown mechanisms that lead to CSD susceptibility and initiate migraine attacks in human patients," offers senior study author Dr. Daniela Pietrobon from the Department of Biomedical Sciences at the University of Padova in Italy.

Dr. Pietrobon and colleagues found that calcium influx and subsequent

glutamate release at cortical pyramidal cell synapses were increased in mice carrying the FHM mutation. Glutamate is the major excitatory neurotransmitter in the brain. The facilitation of induction and propagation of CSD in the FHM mice was completely eliminated when glutamate release was decreased to control levels. Importantly, in contrast with the enhanced excitatory neurotransmission, inhibitory neurotransmission was not altered in the migraine mice.

"Our findings provide direct evidence that enhanced glutamate release may explain the facilitation of CSD in the FHM mouse model. The differential effect of the FHM mutation at cortical excitatory and inhibitory synapses points to a perturbation of the excitation-inhibition balance and neuronal hyperactivity as the basis for episodic vulnerability to CSD ignition in migraine," explains Dr. Pietrobon.

Source: Cell Press