

Mechanisms of Initiation of Cortical Spreading Depression in Migraine Disorders

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Approximately 1 billion people experience migraines, some of which are preceded, and perhaps initiated, by visual auras before pain onset. Auras are caused by slowly traveling waves of inactivity in the visual cortex, called cortical spreading depression (CSD). Cortical inactivity results from a loss of potassium homeostasis in the space surrounding the cortical neurons that is elicited by a rapid increase in cortical neuron activity. Inactivity then slowly propagates through the cortex.

While the consequences of a loss of potassium homeostasis are well-understood, the larger-scale dynamics and mechanisms that initiate CSD remain poorly understood. One hypothesis links mutations of the Na⁺/K⁺ pump, an enzyme essential for potassium homeostasis and present in all brain cells, to CSD initiation. It is unclear how the severity of the pump defects or their spatial distribution affects CSD initiation. We study how spatial variations in pump strength can lead to the initiation of CSD using a computational model of 25 cortical micro-circuits that are coupled through the extracellular space, allowing ions, such as potassium, to diffuse across the network.

Introducing widespread pump defects was sufficient to cause CSD to spread throughout the network. However, high-efficiency pumps could not interrupt the spread. In heterogeneous networks with a mean pump strength above the inactivity threshold, CSD was spontaneously elicited. In networks with larger mean pump strengths, but small variations, CSD was less likely to occur. In networks with larger pump strength variations, CSD occurred but typically in multiple starting locations. For most micro-circuits, the recovery behavior after CSD varied, and some did not recover at all.

Our data suggest that CSD can spontaneously occur in healthy networks that contain randomly dispersed mutations in the Na⁺/K⁺ pump. As a next step, we are testing whether differences in diffusion rates between micro-circuits will affect the rate of CSD.