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Migraine mutations reveal clues to biological basis of disorder

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Fifteen percent to 20 percent of people worldwide suffer from migraines – excruciating headaches often presaged by dramatic sensations, or "auras." By studying a rare, inherited form of migraine, researchers at Vanderbilt University Medical Center have found clues to the biological basis of the painful, debilitating disorder.

In the *Proceedings of the National Academy of Sciences,* Alfred George Jr., M.D., and colleagues report that genetic mutations linked to this rare form of familial migraine alter the function of sodium channels – protein "tunnels" through brain cell membranes involved in the electrical conduction of nerve impulses.

The findings identify cellular events that may prompt migraines – specifically the aura that precedes them – and suggest that medications targeting sodium channels might warrant a closer look as potential treatments for some forms of migraine.

George and colleagues investigated the physiological basis of a severe, inherited form of migraine called "familial hemiplegic migraine type-3" (FHM3). The aura associated with FHM3 often includes a transient weakness or paralysis of one side of the body.

FHM3 is caused by mutations in a sodium channel gene, SCN1A. Researchers in Europe had identified three mutations associated with the condition and contacted George about studying the cellular effects of these mutations.

"We were already studying this gene, SCN1A, in genetic forms of epilepsy," said George, the Grant W. Liddle Professor of Medicine, professor of Pharmacology, and the director of the Institute of Integrative Genomics. "This was a great opportunity to investigate the physiology of SCN1A mutants linked to another episodic neurological disorder."

George and colleagues genetically inserted the mutant sodium channels into cultured human cells and recorded the cells' electrical properties – the key function modulated by sodium channels.

One mutant, called L1649Q, failed to generate any measurable current, indicating that this mutant caused a complete loss of function of the sodium channel.

The two other mutants – L263V and Q1489K – "work as sodium channels but are dysfunctional," George said. "They don't operate normally."

The mutations affected the opening and closing of the channel, a phenomenon known as "gating." Under normal situations, sodium channels are usually closed and open briefly to allow sodium to flow into the cell, which helps generate the electrical current conducted by the cell.

"These dysfunctional sodium channels tend to stay open too long, as if the gating mechanism is stuck," said George. "This problem may predispose neurons to fire more frequently."

The enhanced predisposition to nerve cell firing may be the spark that initiates the aura.

"The aura has been linked to a brain phenomenon known as 'cortical

spreading depression,' which is essentially a wave of inexcitability that travels across the surface of the cortex (the brain's outer layer)," George explained.

"The dysfunctional channels probably aren't directly causing the headache. They're likely involved in causing cortical spreading depression, which then triggers other events ultimately culminating in the severe headache."

Although FHM3 is a rare form of migraine, the findings open up the possibility that more common types of migraine might involve dysfunctional sodium channels. George's team is continuing to study this in other cells and possibly in animal models.

The results also suggest a link between migraine and epilepsy, which often occur together.

"There's been evidence of some connection between migraine and epilepsy, but exactly how they're related is not clear," George said. "Now there's a gene involved in both. So maybe what we've learned here is that there can be a common genetic basis for epilepsy and migraine in some people."

Source: Vanderbilt University