Scientists identify protein that may promote migraines

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A University of Iowa study may provide an explanation for why some people get migraine headaches while others do not. The researchers found that too much of a small protein called RAMP1 appears to "turn up the volume" of a nerve cell receptor's response to a neuropeptide thought to cause migraines.

The neuropeptide is called CGRP (calcitonin gene-related peptide) and studies have shown that it plays a key role in migraine headaches. In particular, CGRP levels are elevated in the blood during migraine, and drugs that either reduce the levels of CGRP or block its action significantly reduce the pain of migraine headaches. Also, if CGRP is injected into people who are susceptible to migraines, they get a severe headache or a full migraine.

The UI study findings are published in the March 7 issue of the *Journal of Neuroscience*.

"We have shown that this RAMP protein is a key regulator for the action of CGRP," said Andrew Russo, Ph.D., UI professor of molecular physiology and biophysics. "Our study suggests that people who get migraines may have higher levels of RAMP1 than people who don't get migraines."

RAMP1 is a normal, required subunit of the CGRP receptor. Russo and his colleagues found that overexpression of RAMP1 protein in nerve cells increased the sensitivity and responsiveness of CGRP receptors to

the neuropeptide -- more RAMP1 made CGRP receptors react to much lower concentrations of CGRP than usual and caused the receptors to respond more vigorously to the neuropeptide.

The UI team also engineered mice to express human RAMP1 in their nervous system in addition to the normal mouse version of the protein. These mice had double the amount of inflammation in response to CGRP than did normal mice. Nerve-induced inflammation is one of the effects associated with migraine headache.

Russo explained that his study raises the possibility that people who have migraines may have subtle genetic differences in the RAMP1 gene that result in increased levels of RAMP1 protein.

"There is clearly a genetic difference between people who get migraines and those who do not, and we think that difference could be RAMP1. Our studies provide a reason to look for variations in the DNA that encodes RAMP1 in humans," he said.

The study also suggests that the mice engineered to produce elevated levels of RAMP1 protein may be a good model for studying migraine and specifically trying to understand how the neuropeptide, CGRP, is working.

The UI team investigated CGRP receptors in the trigeminal nerve, which is responsible for relaying almost all sensory perception, including pain and touch, for the front of the head. The UI findings reinforce the emerging view that CGRP receptors in the trigeminal nerve play a key role in migraine headache.

However, there are other CGRP receptors throughout the body, and elevated CGRP levels are implicated in other types of pain, including arthritis. Russo predicts that his group's findings about RAMP1 will have

implications for pain research beyond migraine headaches.

Source: University of Iowa