

## Study reveals new activation mechanism for pain sensing channel

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A group of scientists at the Scripps Research Institute has identified a mechanism that enables certain compounds to activate a pain sensing protein. The findings could lead to the development of potential new therapies for managing acute and chronic pain. The study was published January 21, 2007 in an advanced online edition of the journal *Nature*.

The researchers found that TRPA1, a protein that helps transmit pain signals, is a direct sensor of reactive chemicals. "While many noxious and pungent compounds were known to activate this pain receptor, we discovered that they do so by directly and irreversibly binding to the cysteine amino acids of this protein," said Ardem Patapoutian, a Scripps Research scientist whose laboratory conducted the study. "Our study shows that TRPA1 activation is directly linked to chemical insult."

"Cysteines, one of the twenty building blocks of all proteins, are known to undergo oxidation/reduction reactions," Patapoutian continued. "Somehow the TRPA1 protein is tuned to sense cysteine modifications. In fact, any cysteine reactive agent seems to activate TRPA1, although we don't know exactly how cysteine binding translates into ion channel activation."

But this activation mechanism comes with an interesting property.

"Generally, compounds that activate ion channels bind in a lock-and-key mechanism that is readily reversible," said Lindsey Macpherson, another author of the study and a Ph.D. candidate in the Scripps Research

Kellogg School of Science and Technology. "The mechanism by which noxious compounds activate TRPA1 is unique. For example, compounds that activate an ion channels through a lock-and-key mechanism have structural similarity. TRPA1 activators have no structural similarity; instead, they share a common potential for chemical reactivity, and their binding is long-lasting."

TRPA1 is not unique among proteins to be activated by cysteine modifying agents, the study noted. Another signaling protein known as Kelch-like ECH-associated protein 1 (KEAP1) is activated by many of the same compounds that activate TRPA1; KEAP1 is a sensor for oxidative damage from free radicals and upregulates expression of antioxidant enzymes. Apparently, reactive compounds can activate at least two pathways through cysteine modification as a warning against cell damage, the study concluded.

"Our findings, which are the result of a successful collaboration with the Ben Cravatt and Peter Schultz labs at Scripps Research, show that modification of reactive cysteines within TRPA1 can cause channel activation," Macpherson said. "Our research efforts are now aimed at further understanding how binding of these compounds activate the channel, and identifying the physiological role of TRPA1 in sensing oxidative stress." The protein is currently being investigated by several pharmaceutical companies as a potential target for chronic pain, Patapoutian noted.

Source: Scripps Research Institute

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