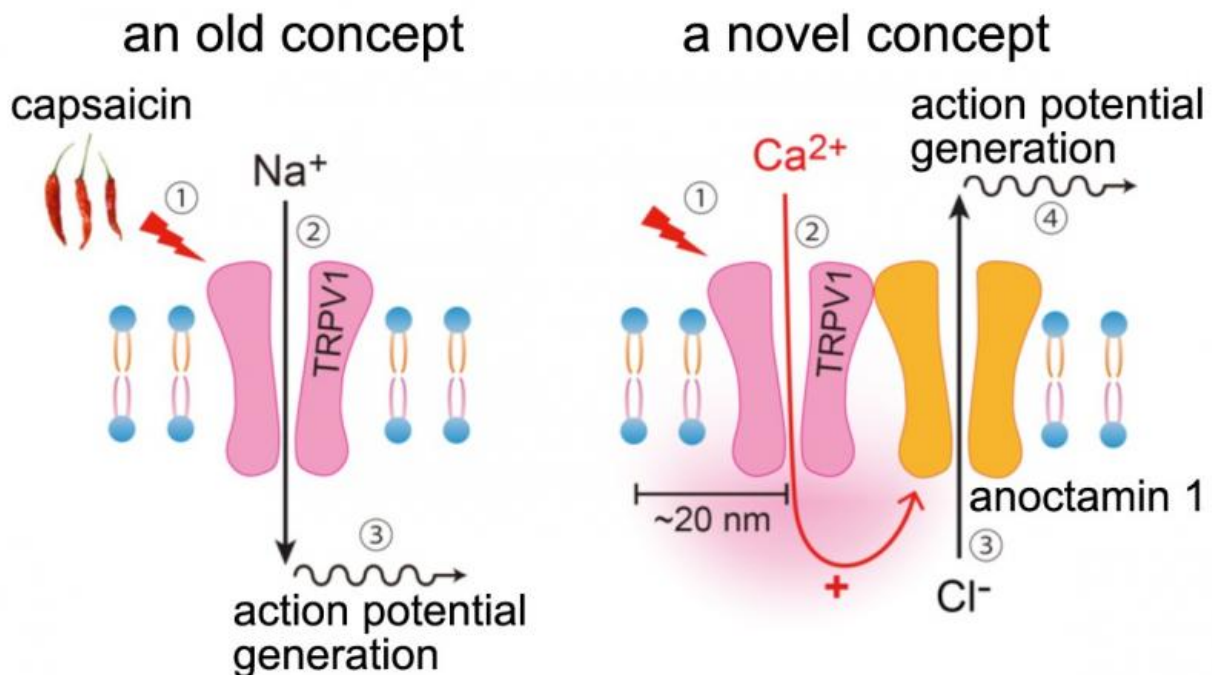


Enhancing mechanism of capsaicin-evoked pain sensation

April 6 2015



Old and novel mechanisms for nociception involving TRPV1 are shown. Credit: National Institute for Physiological Sciences

Drs. Takayama and Tominaga in National Institute for Physiological Sciences (NIPS) (Okazaki Institute for Integrative Bioscience) clarified that an interaction between capsaicin receptor TRPV1 and chloride channel anoctamin 1 causes enhancement of the capsaicin-evoked pain sensation in mice in collaboration with Dr. Uta (Toyama University) and

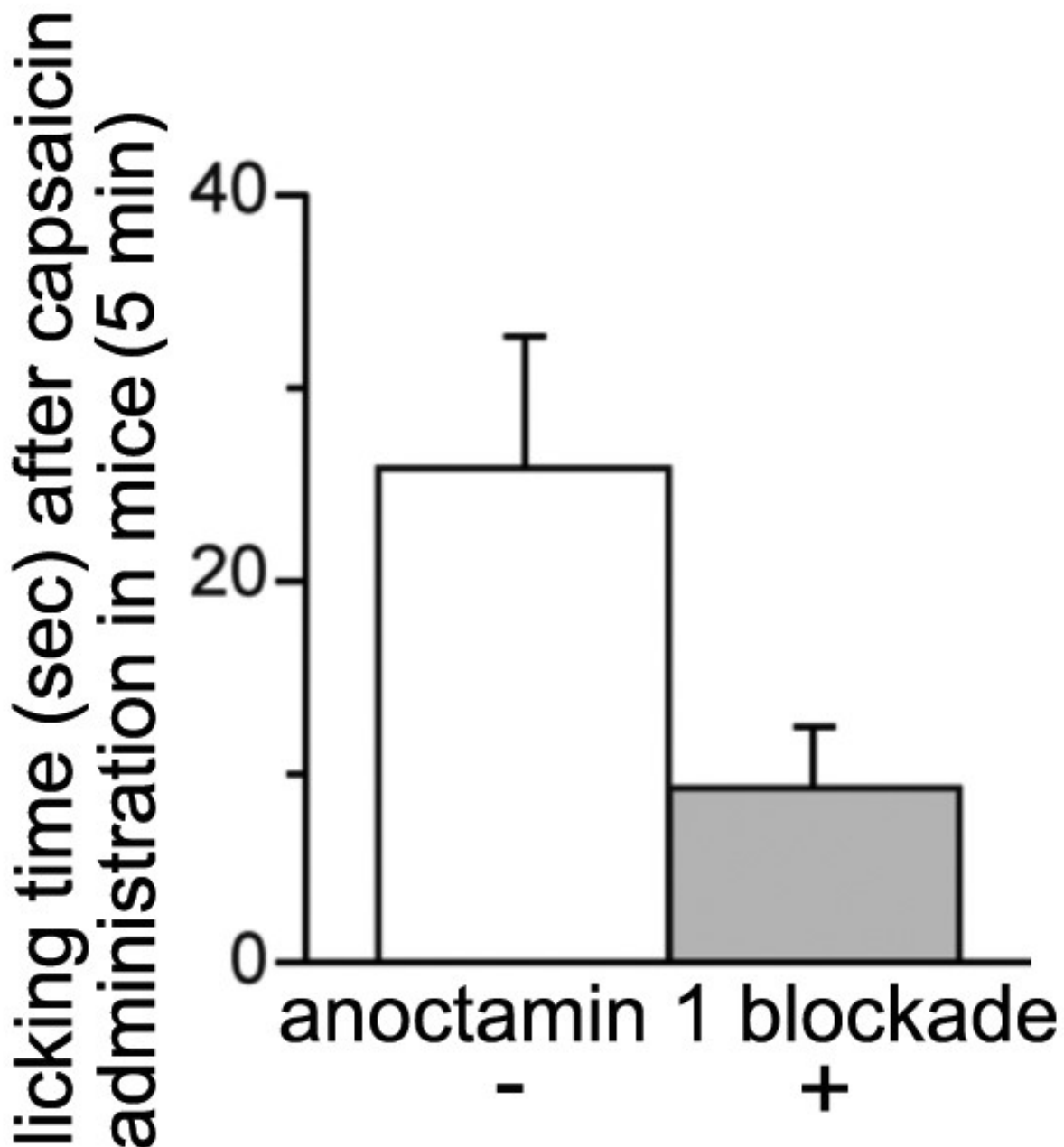
Dr. Furue (NIPS). This result will be published in the *Proceedings of the National Academy of Sciences* of the United States of America.

It has been well known for more than 10 years that capsaicin contained in capsicums causes pungent (pain) sensation through activation of capsaicin receptor TRPV1 expressed in sensory neurons. Anoctamin 1 is also known to be involved in nociception independent of TRPV1. Drs. Takayama and Tominaga found that nociceptive responses are increased by anoctamin 1 activated by TRPV1 which binds to anoctamin 1 in the analyses using sensory neurons and [spinal cord](#) of mice. In addition, they proved that chemical blockade of anoctamin 1 is effective for relief of pain induced by TRPV1 activation.

The research group focused on the two ion channel proteins, TRPV1 and anoctamin 1 in mouse sensory neurons. And, they found that anoctamin 1 activation is accompanied by TRPV1 activity and that this sequential channel activation enhances capsaicin-evoked [pain sensation](#).

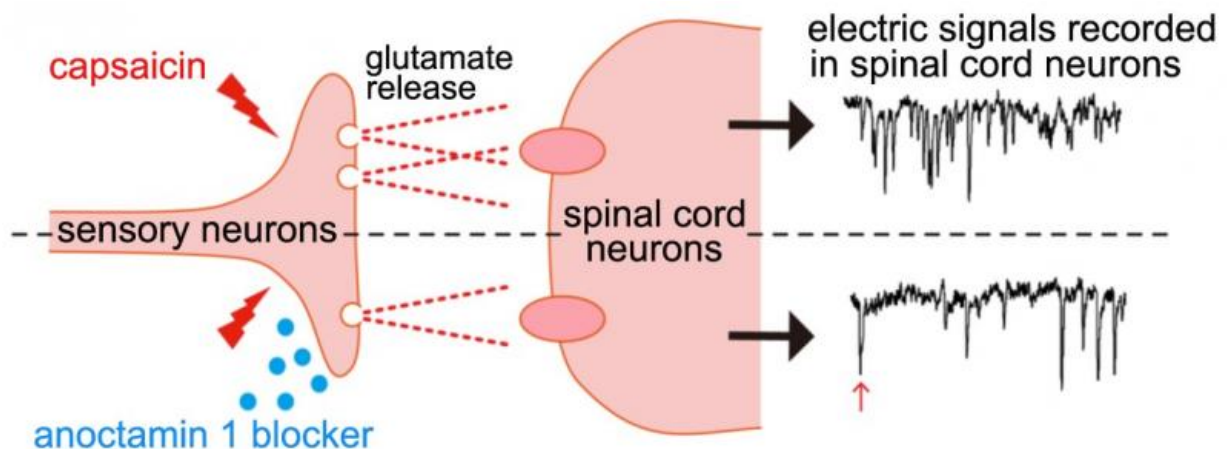
Capsaicin-evoked burning pain sensation is induced by neural excitation through activation of TRPV1 in sensory neurons. While hot water activates TRPV1, capsaicin is stronger stimulus for TRPV1. Because TRPV1 is a non-selective cation channel, people believed that Na⁺ ion influx through TRPV1 pore causes depolarization, leading to the action potential generation (Figure 1, left). In this study, however, the research found a novel pain-enhancing mechanism in which anoctamin 1 activated by Ca²⁺ ions entering cells through TRPV1 causes chloride efflux because intracellular chloride concentrations are high in the sensory neurons, which leads to further depolarization. In addition, the research group found that the functional interaction is based on their physical binding, indicating that Ca²⁺ ions work in the nanodomain within 20 nm distance (Figure 1, right). Furthermore, the research group observed that pain-related licking behaviors in mouse hind paws given capsaicin were inhibited by an anoctamin 1 blocker (Figure 2). Protein produced in the

sensory neuron cell bodies are believed to be transferred not only to the peripheral [sensory nerve endings](#), but also to the presynaptic terminals of the primary afferent neurons. Nociceptive signal transmission from primary afferent neurons to the second neurons in spinal cord was also reduced by anoctamin 1 blockade. Thus, anoctamin 1 blockade is useful to reduce the TRPV1-mediated pain responses.



Anoctamin1 blockade inhibits capsaicin-evoked pain-related behaviors. Credit: National Institute for Physiological Sciences

An old mechanisms (left): 1) capsaicin activates TRPV1, 2) Na^+ ions enter sensory neurons through the TRPV1 pore, 3) action potentials are generated (neurons are excited). A novel mechanism (right): capsaicin activates TRPV1, 2) Ca^{2+} ions enter sensory neurons through the TRPV1 pore, 3) because intracellular chloride concentrations are high in the [sensory neurons](#), chloride ion efflux is induced by anoctamin 1 activated by Ca^{2+} ions within 20 nm distance from TRPV1 through physical binding of the two proteins, 4) action potentials are generated. Thus, capsaicin-induced inward currents are composed of two components: TRPV1-mediated Na^+ influx and anion efflux through anoctamin 1 activated by Ca^{2+} ions entering cells through TRPV1.



Nociceptive information transmission upon capsaicin application was inhibited by an anoctamin 1 blocker. Credit: National Institute for Physiological

Mice keep licking their hind paws upon capsaicin injection. Time spent for licking for 5 min was reduced by concomitant application of an anoctamin1 blocker.

Nociceptive signals are transmitted from the primary afferent neurons to the second neurons in spinal cord with a neurotransmitter glutamate. The electric signals can be observed (a red arrow). Capsaicin increases such electric signals. However, the increase was reduced by an anoctamin 1 blocker.

More information: Pain-enhancing mechanism through interaction between TRPV1 and anoctamin 1 in sensory neurons, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1421507112

Provided by National Institutes of Natural Sciences

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