A sense of touch: ASICs are the receptor for a proton synaptic messenger between Merkel cells and an afferent nerve

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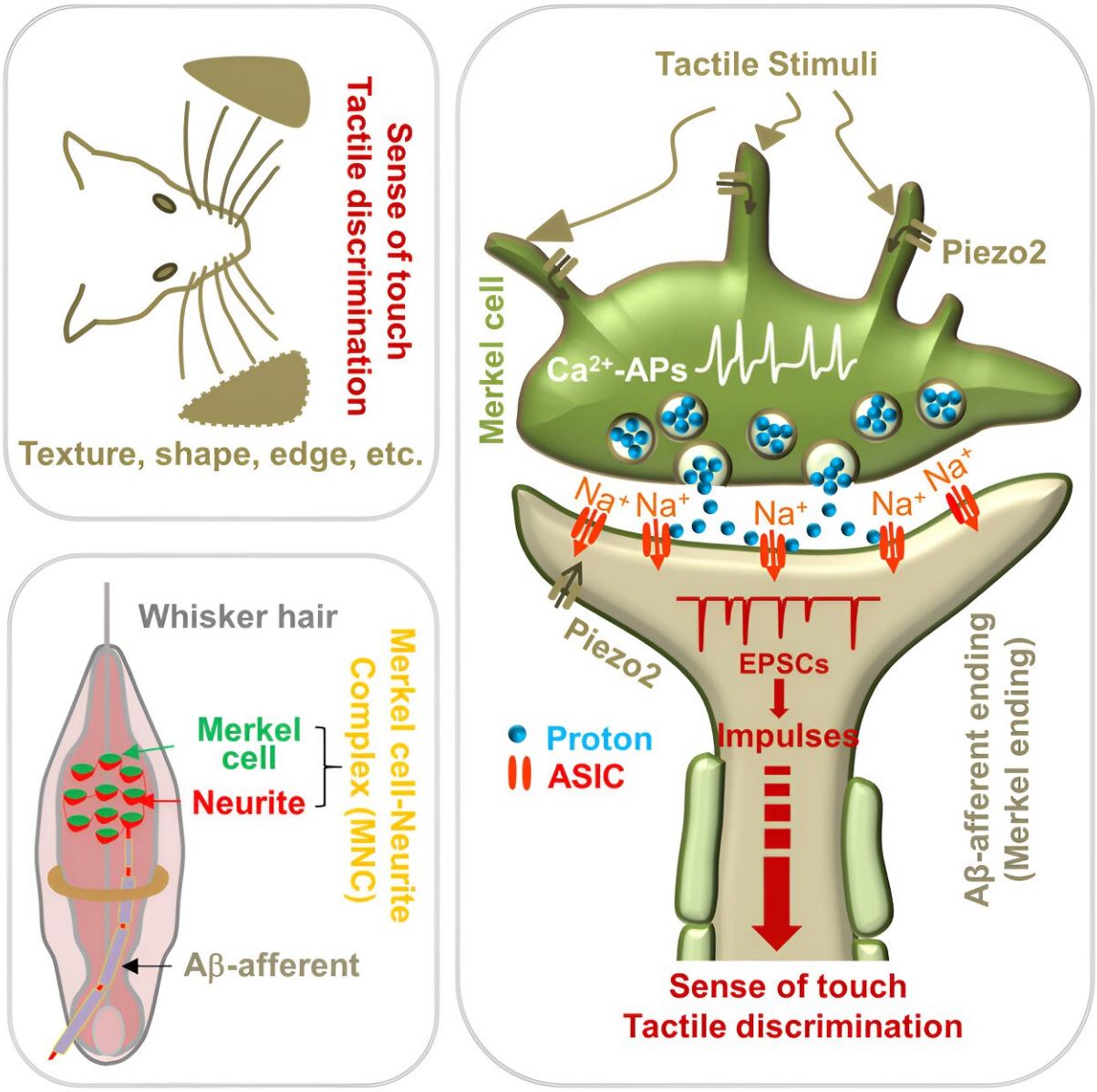

Credit: *Neuron* (2024). DOI: 10.1016/j.neuron.2024.01.018

Transduction is the changing of one form of energy into another, such as a spoken voice changed into radio waves by a cellphone.

Ten years ago, three research teams published a breakthrough—the first description of the molecular mechanism for transduction in fingertip sensory Merkel cells that can transduce gentle touch, a mechanical force, into an electric current. That discovery won a 2021 Nobel Prize in Physiology or Medicine for one of those team leaders, Ardem Patapoutian, Ph.D.

Yet a mystery remained.

How does the tactile signal at those fingertip sensory Merkel cells travel across the empty synapse space from the Merkel cells to the tip of a nerve cell? Jianguo Gu, Ph.D., and colleagues at the University of Alabama at Birmingham now have answered that mystery in a study published in the journal *Neuron*.

Gu reports that protons are the signals that cross the synapse space from a Merkel cell to an Aβ-afferent nerve, and his UAB team identified the receptors in the nerve that sense the protons as ASICs, or acid-sensing ion channels. Protons trigger the ASIC to open its transmembrane channel, which allows a flood of sodium ions, or Na^+, into the nerve. This, in turn, can trigger action potential impulses that rapidly propagate up the afferent nerve toward the brain.

"Protons have never been previously reported as principal transmitters in

any synapse, and their role as the principal transmitters for tactile transmission at Merkel cell-neurite complexes is highly unique," Gu said. His discovery adds protons to the list of well-known neurotransmitters, like glutamate, GABA, acetylcholine, dopamine or serotonin.

The small, oval Merkel cells are key to tactile discrimination, the ability to differentiate the physical properties of objects, such as texture, shape and edges. As noted by the Nobel Prize organization in 2021, "The sense of touch, initiated by the detection of mechanical force, provides us with the recognition of texture, size and shape of objects, as well as tactile and vibration sensitivity. This sense, for example, allows us to recognize the softness of a pillow, gentle caress of the skin or the feeling of a breeze."

While primate fingertips have the most Merkel cells, making a fingertip the most sensitive part of the human body, in non-primate mammals the most sensitive touch receptors are whiskers. Thus, the whisker follicle with its numerous Merkel cells and exquisite sensitivity is biologically analogous to the human fingertip. To study the conveyance of tactile signals, Gu's team studied whisker hair follicles from rodents.

In the whisker follicle, the tip of each afferent nerve splits into about 28 smaller neurites, thin strands protruding from the end of the nerve. Each neurite reaches out to form a synapse with a Merkel cell in the front part of the whisker hair follicle.

To measure reception of a tactile signal from a Merkel cell, the UAB researchers achieved patch-clamp recordings at a heminode—an accessible spot for a patch-clamp on the neurite between the Merkel cell synapse and the tip of the afferent nerve—and at the first node of Ranvier, an accessible site on the afferent nerve just below the tip of the nerve.

This was a challenging feat, Gu says. "Patch-clamp recordings have never previously been performed on Aβ-afferent axons near Merkel-neurite synapses due to technical difficulties because most parts of Aβ-afferent axons are heavily myelinated and inaccessible to patch-clamp recording electrodes."

The patch-clamp uses a glass pipette drawn out to extreme thinness to clamp onto the membrane of a neuron. After a hole is punched through the membrane, the patch-clamp is able to measure electrical currents or membrane potential in the whole cell.

In the study, Merkel cells were evoked by mechanical stimulation or depolarizing currents, while the patch-clamps measured responses at the neurite heminode and first node of Ranvier in the afferent nerve.

Multiple lines of evidence showed that ASICs are the receptors on the neurite for tactile discrimination signals from Merkel cells, Gu and colleagues say.

First, electrophysiology showed the receptor appeared to be a Na^+-selective channel, a class of ion channels that would include ASICs. Second, the researchers found that ASIC pharmacological and toxin blockers prevented reception of the Merkel cell signals at the afferent nerve, and genetic deletion of one of the ASIC subunits, to make it less effective, reduced reception of the signals in the afferent nerve. Third, immune fluorescence imaging showed that ASICs are expressed at the Aβ-afferent terminals that innervate the Merkel cell-neurite complexes.

Fourth, focal application of protons to the neurites of Merkel cell-neurite complexes directly evoked excitatory currents in the afferent nerve. Fifth, neutralizing the endogenous protons using alkalizing agents or preventing the release of protons from Merkel cell vacuoles blocked transmission of the tactile signal from Merkel cells to the afferent nerve.

A final piece of evidence came from animals in a tactile recognition behavioral test.

When a rat or mouse is put into an open field box that contains two identical smooth objects placed in diagonal corners, they spend equal amounts of time using their whiskers to palpate and recognize each object. If one of the smooth objects is then replaced by an object with an identical shape but a rough surface, when the rodents are returned to the open field box they spend much more time palpating the novel rough-surface object, compared to the smooth object.

The UAB researchers found that giving rats two different pharmacological blockers of ASICs eliminated that preference for the novel rough surface object, suggesting that the animals treated with ASIC blockers were unable to discriminate the rough object as a novel tactile stimulus.

To further support the idea that ASIC channels are involved in whisker tactile discrimination, the researchers tested mice that had the deletion of one of the ASIC subunits. In the tactile discrimination experiments, in contrast to controls, the mice with that ASIC subunit deletion showed no preference to palpate the novel object. As it did in the rat experiment, this suggested that the ASIC-mutant mice could not discriminate the rough-surface object as a novel tactile stimulus.

"Initially, ASICs were thought to be mechanical transducers of mammals," Gu said. "However, numerous studies over the past several decades could not establish that ASICs are mechanical transducers in mammals. In the present study, we have discovered that instead of serving as mechanical transducers, ASICs mediate fast excitatory synaptic transmission at Merkel cell-neurite complexes to encode tactile signals and enable tactile discrimination."

Gu, one of the three team leaders 10 years ago who first described the molecular mechanism for transduction in fingertip sensory cells that can transduce gentle touch into an electric current, is the Edward A. Ernst, M.D., Endowed Chair and director for Pain Research in the UAB Department of Anesthesiology and Perioperative Medicine in the Marnix E. Heersink School of Medicine.

Co-authors with Gu in the *Neuron* study, "ASICs mediate fast excitatory synaptic transmission for tactile discrimination," are Akihiro Yamada, Jennifer Ling and Ayaka I. Yamada, UAB Department of Anesthesiology and Perioperative Medicine; and Hidemasa Furue, Hyogo Medical University, Nishinomiya, Japan.

More information: Akihiro Yamada et al, ASICs mediate fast excitatory synaptic transmission for tactile discrimination, *Neuron* (2024). DOI: 10.1016/j.neuron.2024.01.018

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