

Nobel Prize in medicine awarded to the discovery of the cellular mechanism behind the sense of touch

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This year the Nobel Committee for Physiology or Medicine awarded the prize in medicine to two researchers from the US for their efforts in elucidating the molecular and genetic mysteries behind the sense of touch. The recipients, Dr. David Julius of the University of San Francisco and Dr. Ardem Patapoutian of Scripps Research in La Jolla, California, were jointly awarded this week “for their discoveries of receptors for temperature and touch.”

Professor Abdel El Manira, a neuroscientist and member of the Nobel committee, explained that “without the receptors we would not be able to sense our world, to feel the urge to pull our hand from a flame, or even stand upright. The discoveries have profoundly changed our view of how we sense the world around us.”

There is, perhaps, an unstated irony that the Nobel Committee has decided to award, during such a cataclysmic pandemic where people have been placed in lockdowns and asked to social distance to stem the tides of repeated infections and deaths, their prestigious prize to an issue that is literally skin deep.

But a closer look leads one to appreciate the importance of these discoveries that have eluded scientists until recently. The findings offer a far more compelling evaluation of human society and provide a deep dialectical connection between the physical world and life. In other words, life, more than just replicating, interacts with the world. But it does so through the confines enforced on it by the physical world. And through that interaction, it learns to change.

Dr. Patapoutian, in a review article published in the journal *Nature* last year, wrote, “From the sound of a whisper to the strike of a hammer on a finger, many

familiar environmental cues occur as mechanical forces. *Mechanotransduction*, the conversion of mechanical perturbations into electrochemical signals, is conserved across all domains of life. It is possibly the most ancient sensory process and may have protected early protocells from osmotic and mechanical forces that threatened to break their membranes.”

The award for understanding the mechanism behind touch and temperature is only the latest, perhaps the last, recognized by the Nobel Committee. During the press conference following the announcement, Dr. Julius said, “It’s been the last main sensory system to fall to molecular analysis ... for things like temperature and pressure sensors, we really didn’t have examples of the types of molecules [used in vision and smell] that we could look for.”

In 1961, George von Békésy, a Hungarian biophysicist, was awarded the Nobel prize for his work on the impact of sound on the human cochlea, translating the frequencies of sound waves into nerve signals leading to the brain. In 1967, three recipients, Ragnar Granit, Haldan Keffer Hartline and George Wald, shared the award “for their discoveries concerning the primary physiological and chemical visual process in the eye.” Then, in 2004, Dr. Linda Buck and Dr. Richard Axel were recognized for discovering hundreds of receptors in the nose for odors and how the olfactory system was organized and connected to the brain.

Dr. Julius’s discovery built on the work that Hungarian researchers in the late 1940s first conducted. The use of high doses of capsaicin, the active ingredient in chili peppers that causes the sensation of heat, rubbed into laboratory mice relieved pain. Though drug

discoveries followed that could help lower body temperature, decrease inflammation and help blood vessels dilate, no one understood how these mechanisms worked until Dr. Julius and his team set out to systematically find the molecules responsible for sensing capsaicin.

After an exhaustive trial and error process, his team identified one gene in sensory nerve cells that responded to the “burning” ingredient. That gene, now known as TRPV1, instructs the cell to build a protein known as an *ion channel* that allows the cell to perceive *heat* as painful and react to it.

Ion channels are particular proteins (or gates) lodged into a cell’s membrane that allows physical communication with the cell’s external environment through the influx and efflux of various ions. These ions act as chemical signals that lead to a cascade of secondary and tertiary signals to which the cell responds, leading to a concerted response by the living organism.

Julius and Patapoutian’s work converged, though independently, when they both used menthol to discover the receptor for sensing *cold*, named TRPM8, including several others that have intermediate responses.

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Patapoutian then set to conduct research to identify similar ion channels that involved response to mechanical forces. This entailed working with cell lines that emitted a small burst of electrical signals when prodded with a micropipette, a fine-tipped instrument for collecting tiny quantities of liquids. Through the iterative process of switching off genes in these cells, they identified the crucial protein for sensing pressure, an ion channel they named PIEZO1.

In a thought-provoking statement reviewing the discovery of numerous mechanical-electrical ion channels, authors Dr. Dominique Douguet and Dr. Eric Honoré, writing in the journal *Cell*, said, “The opening of mechanosensitive ion channels at the plasma membrane of mammalian cells, in the microsecond range, is the earliest event occurring upon mechanical stimulation.” Precisely, the shear forces that stretch and bend a cell lead to opening these gates with the ensuing response that converts the mechanical stimulation to a chemical reaction that leads to the formation of a

sensation at the molecular level with exorbitant speed.

Since then, numerous mechanically activated ion channels have been identified that provide a conscious sense of touch and the unconscious sense associated with blood pressure regulations and other organ functions involved in the life process. This ability for our cells to sense mechanical forces is a fundamental process conserved in the evolution of life.

As the Nobel Committee statement noted, “The laureates identified critical missing links in our understanding of the complex interplay between our senses and the environment. The groundbreaking discoveries ... by this year’s Nobel Prize laureates have allowed us to understand how heat, cold, and mechanical forces can initiate the nerve impulses that allow us to perceive and adapt to the world around us.”

However, Professor Patrick Haggard of University College London’s Institute of Cognitive Neuroscience said it best. “It is about the closest scientists have got to a truly mechanistic understanding of our own conscious experiences.”



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