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Mini Review

Nobel Prize in "Physiology or Medicine" for 2021

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Conspectus

Human experiences and historical explanations: We, homo sapiens sense heat, burning taste of chili peppers, cold, pain and touch inadvertently. For a 16th century man, it was obvious and convincing explanation offered (then sufficient) was that it was a natural phenomenon. A painful burning sensation when a foot is touching an open flame was rationalized by René Descartes, a 17th century philosopher, with a concept that particles of fire send a mechanical signal by pulling a thread between the skin and brain. In the 1880s, distinct sensory spots on the skin were invoked which react to specific thermal (heat or cold) and touch (pressure/mechanical) stimuli.

Nobel prize winning research: Updated information, knowledge, embedded intelligence, discoveries and inventions push towards peace of life in human subjects in their interactions with inside and outside environments. The scientific outcome for good of humankind has been honoured with Noble awards for scientists who are responsible for it. During the period 1901 to 1945, four Nobel Prizes were awarded in Physiology or Medicinefor knowledge extraction about neurons and nervous system. The focal themes were elucidation of the structure of the nervous system, anatomical description of the somatosensory assembly (1906), function of somatosensoryneurons (1932), sensory function of the Vagus nerve in reflexes/ aortic mechanisms in the regulation of respiration (1938), differentiated functions of single somatosensory nerve fibers that react to distinct stimuli, like in the responses to painful and non-painful touch (1944).

During later period of 1950s, it was found that capsaicin induces ionic currents and act on sensory nerves.

Unsolved riddles: What was not clear by then was

- How the chemical actually exerted this function?
- Was the ion channel itself function as a transducer?
- What are the ultimate sensors of touch and mechanical stimuli in humans?
- How it is converted into electrical impulse (action potentials) within the somatosensory nerve fibres?

David Julius's research: David Julius discovered TRPV1, the calcium ion channel which senses temperatures greater than 110 degrees F (thermal energy) as well as capsaicin (in chili peppers) burning (hot)taste/ pain. Both are transmitted to the brain as a sense of heat. His seminal contributions wide-opened the door to a molecular understanding of thermo-sensation. The near-atomic scaleaccurate

structure of TRPV1 was reported in 2013 using cryo-electron microscopy. TRPV1, TRPA1, TRPM2 and TRPM3 ion channels collectively act as warm sensors. This research paved way in the design of new drugs for critical pain relieving.

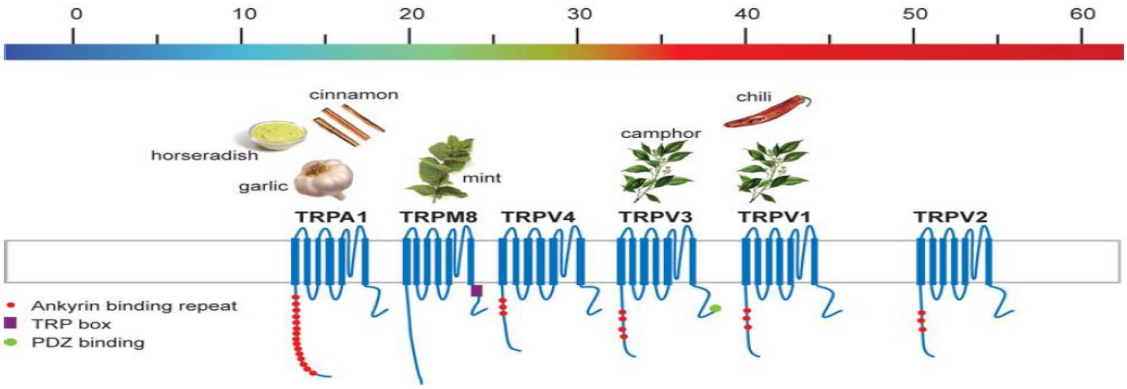
Ardem Patapoutian's research: PIEZO ("piesi" means pressure in Greek) proteins belong to largest transmembrane ion channel subunits containing around 2,500 amino acids. PIEZO1 gene regulates critical physiological processes like blood pressure, respiration and urinary bladder control. It also senses mechanical forces in endothelial and red blood cells. In essence, PIEZO1, PIEZO2, and TRPM8 receptors recognize strain, menthol and (cold) temperatures.

The mutations/function loss in the PIEZO2 gene result in distal arthrogryposis (severely uncoordinated body movements, abnormal limb positions etc.) and deficiency in touch (texture, hair deflection/tactile and vibration) sensation.

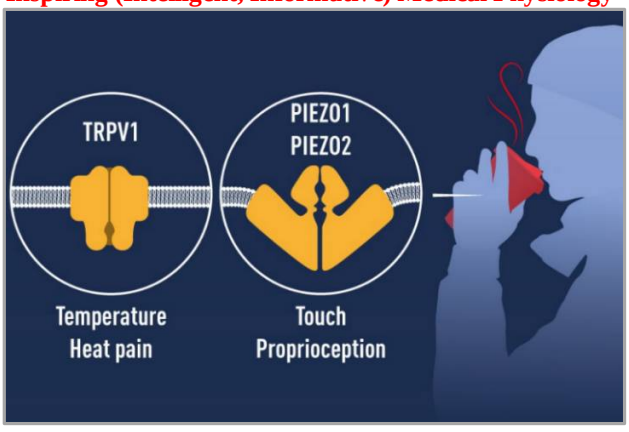
Nobel Prize in Physiology or Medicine of 2021: David Julius of University of California and Ardem Patapoutian of Scripps Research shared NP.Med.2021for the ingenious discoveries of genes and receptors which sense temperature, taste-/burning sensation of Capsaicin and touch/pain in human beings.

Prospects to man-kind in future: Today's scientific-knowledge (including method-bases) with Fourth Paradigmtools is the take-off pad for upcoming explorations. The greatest benefit to life-on-earth lies in interplay between natural and artificial intelligence, real and artificial life, Moon-to-Mars-mission, other our-solar system curiosity driven exploration of ingenious perseverance programs and evolution of nature.

Graphical Abstract



Inspiring (Intelligent, Informative) Medical Physiology



(Insp. Med. Physiol. ; Imp.)

Mother's touch

Ion-channels -- Proteins ---- Genes

Keywords: Nobel Prize-2021-Physiology or Medicine; human sensing-Thermal; taste/burning-of-Capsaicin; touch; ion-channels; TRPV1; TRPM8; PIEZO1;PIEZO2; genes-mutation; Loss-of function; Clinical;

INTRODUCTION

Alfred (Bernhard) Nobel was a research chemist, linguist and a peace monger. His father, Immanuel Nobel was an engineer/inventorand mother Carolina Andriette (Ahlsell) Nobel was a homemaker. Nobel was born on Oct 21,1833in Stockholm, Sweden. He spoke five languages at the age of 17 and also had experience in writing poetry and drama later. Alfred acquired skills of an engineer, technocrat and entrepreneur. Dr. Nobel's major part of research and industrial chores were in explosives (nitro-glycerine) and dynamite. During his career, 350 patents of different countries (like 39 Swedish and 58 English) were sanctioned. With a passion to finance pure science endeavours and honor intellectuals benefitting the human race with their contributions, he instituted, in 1895, a set of prizes called 'Nobel Prize' with completely his personal property worth of 31 million SEK (today it is 1702 million SEK).

The will of Dr Nobel came into force in 1901 with three pure science –Physics, chemistry and Physiology or Medicine—annual awards. The two more disciplines included for Nobel prizes are 'Literature' and 'Peace'. The prizes are given to contributions emanating 'Greatest benefit to humankind'. The Nobel prize is the highest honour to a Scientist for the intellectual persuasion with no known application or utility at the time of on-going experimentation. It is it (That is Nobel Prize is Nobel Prize); no comparison in flare and reputation or in terms of science per Dollar (Price).

Nobel prizes in Physiology or Medicine [1]: Every year, one person or not more than three individuals, who contributed to most important discovery/invention within the domain of Physiology or Medicine win(s) the Nobel prize. If none of the research outcomes are suitable, the prize is not given that year. During the period 1901 to 2021, one hundred twelve times noble prizes in PM have been announced and the number of Nobel Laureates being 224.

Physiology or MedicineNobel awards (1901 to 2021)

# NPs	# Scientists sharing	# NLs
39	1	39
34	2	68
39	3	117
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112		224

$$ NL	Age	Year	Nobel Laureate
Oldest	87	1966	Peyton Rous
Youngest	32	1923	Frederick G. Banting

# Women Nobel Laureates	12

NPs not awarded in years	1915, 1916, 1917, 1918, 1921, 1925, 1940, 1941 1942

2021 Nobel Prizein Physiology or Medicine: This year's Nobleprize [2] is shared between Dr (Prof)David Julius of University of California and Dr (Prof) Ardem Patapoutian of Scripps Research for the ground breaking ingenious discoveries of receptors (ion-channels; genes) in human being to sense temperature (warmth, cold, chill), taste-/burning sensation of Capsaicin and feel of touch (affectionate, discriminative, pain, mechanical). A historical/ early science perspective and state-of-knowledge perseverance follow (vide infra).

Table 1.1 Focal theme of Nobel Prize for Physiology or Medicine in 2021

! **Discovery**	☞ Receptors for temperature, capsincin and touch	🕮 David Julius 🕮 Ardem Patapoutian

Human experiences with sense organs: The sense (eye, ear, nose, tongue, skin) organs of a human-being interact with and assimilate only the stimulus (type, range) they are capable of in the external environment from different sources (visible-objects, sounds, smell/odour, taste, touch). The signals (corresponding to different forms of single energy) are transmitted through CNS to brain which processes and responds in the programmed manner. The knowledge of what type of signals are these, how they are sensed, path of elaboration is a long story intertwined with scientific advances to understand the evolution of life-processes and environment, both external and internal.

Human sense organs, CNS and brain

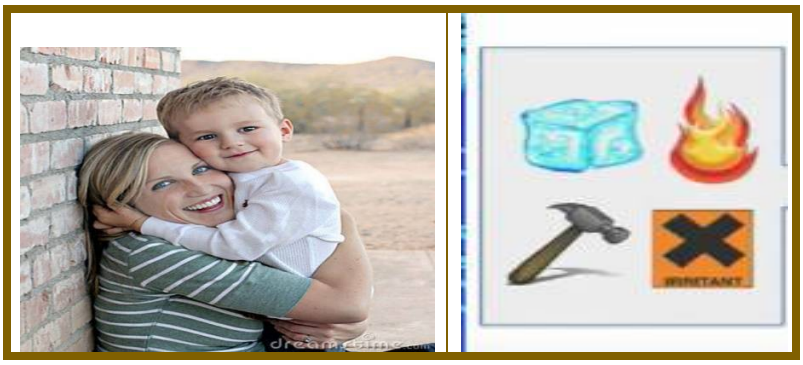
Human experience of Heat, Cold and touch: We, homosapiens sense heat, cold and touch; it is obvious. The experience of walking barefoot across a lawn on a hot summer's day is a feel of heat of the sun, the

caress of the wind, and the individual blades of grass underneath the feet. A man in 16th century should have a convincing and sufficient explanation that it is natural phenomenon.

René Descartes, 17th century philosopher, depicted that when a bare foot is touching an open flame, thenparticles of fire send a mechanical signal by pulling a thread between the skin and brain. In the 1880s, distinct sensory spots on the skin react to specific thermal (heat or cold) and touch (pressure/mechanical) stimuli,

Burning sensation of capsaicin [3,4], the pungent ingredient of chili peppers: The chemical compound capsaicin causes the burning sensation while eating spicy food, biting raw chillies, or even when one comes into direct contact. Further, gustatory sweating was induced when hot peppers are in touch with lips, crunched in the mouth or mouthful of them are eaten by accident. During later period of 1950s, it was found that capsaicin induces ionic currents and act on sensory nerves. What was not clear then how this chemical actually exerted this function and was the ion channel itself function as a transducer.

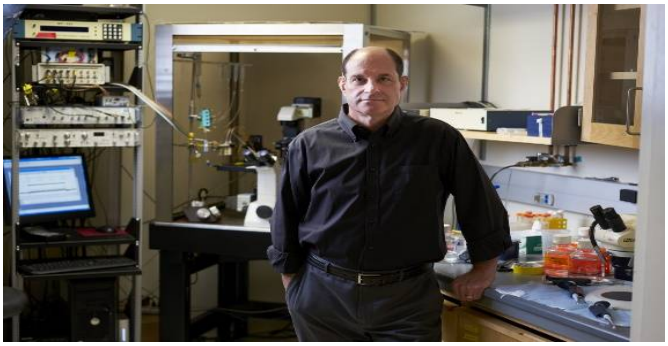
Touch: The sense of touch in humans is natural (divine bliss) and one is fond of. It remained tobe a long-standing mystery to The Science; yet every one continues with a feel that it as an obvious phenomenon but is proud of. In spite of abundant accumulated data and information, the sense of touch is not understood at molecular level till recently. The targets for stimulus of touch are diverse being skin and also internal organs of human body. The light pressure generated by human touch (affectionate, discriminative) including mothers hug to the infant /child is different from mechanical punch with devices/accidents sometimes crossing the levels of threshold of tolerable pain. To add to list of mechanical sense of touch, sound (hearing), sheer stress (cardiovascular tone) etc. play a critical role in on-going-life processes.



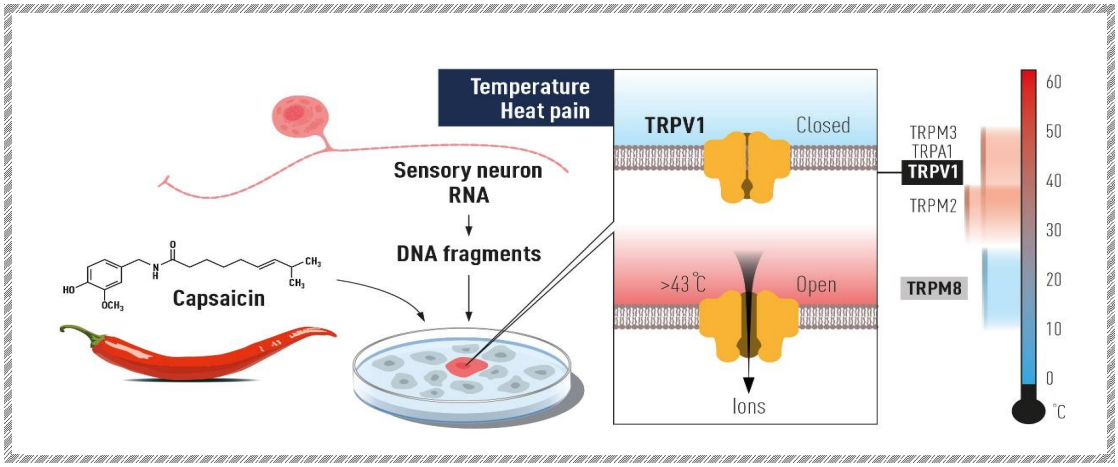
Earlier Nobel prizes in neuro-science: In 1906, Camillo Golgi and Santiago Ramón y Cajal won Nobel Prize [1] for elucidation of the structure of the nervous system, and anatomical description of the somatosensory assembly. The discovery of description and function of (somatosensory) neurons brought noble prize to Edgar Douglas Adrian and Sir Charles Scott Sherrington in the year 1932. The results of studies of the sensory function of the vagus nerve in reflexes and aortic mechanisms in the regulation of respiration was the focal theme of 1938 Nobel prize. Joseph Erlanger and Herbert Gasser were awarded 1944 Physiology or Medicine Nobel prize for their researches on differentiated functions of single somatosensory nerve fibers that react to distinct stimuli, like in the responses to painful and non-painful touch.

Unsolved riddles: What are the ultimate sensors of touch and mechanical stimuli in humans? How it is converted into electrical impulse (action potentials) within the somatosensory nerve fibres?

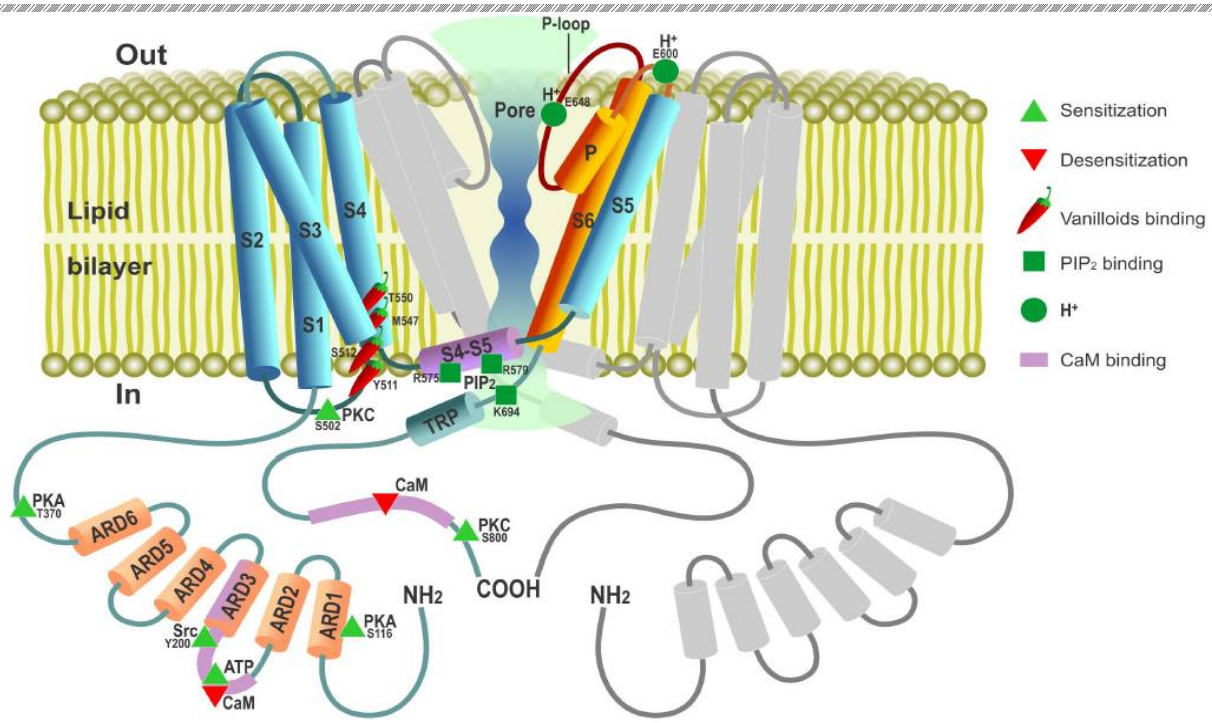
David Julius era [5]: David Julius of University of California made up his mind to carry out unbiased functional- screen based DNA fragment encoding the protein capable of reacting to capsaicin. The assumption was a single gene can confer capsaicin sensitivity in cells that are normally insensitive. Julius along with a postdoctoral researcher, Michael J. Caterina, made a cDNA library from rodent dorsal root ganglia which contain the cell bodies with capsaicin-activated sensory neurons. Capsaicin-insensitive cells were transfected with batches of these cDNAs and eventually a single cDNA clone was isolated which was found to contain/ confer responsiveness to capsaicin.

Affiliation	**Nobel Laureate (Med)** **Photo** **Date & place of birth**	**Share**
University of California, San Francisco, CA, USA	David Julius  Born: 4 November 1955, New York, NY, USA	1/2
	https://www.nobelprize.org/prizes/medicine/2021/julius/facts/	

The identification of single gene (TRPV1) started a new era in molecular level sensing. Deeper studies brought out that the gene encodeda novel ion channel proteinlater called TRPV1.



TRPV1: Transient receptor potential (pronounced as"trip" and TRPV1 is also referred as the vanilloid receptor (VR) number 1). These calcium-permeable ion channels consist of six related protein sub-families which are involved in a variety of pathophysiological function, and disease development process. TRPV1 is identified by expression cloning using the "hot" pepper-derived vanilloid compound capsaicin as a ligand.



Courtesy of Ref [4]

- TRPV1 channel is a tetramer composed of four TRPV1 subunits arranged around a central ion-conducting aqueous pore
- Cylinders – a-helical segments, including S1…..S6 trans membrane domains
- P pore(P)-loop a-helix,
- ARD1-6 – ankyrin-repeat domains,
- Parts of TRPV1 subunit contributing to ion-conducting pore are presented in burgundy-orange

TRPV1 Response to heat: The critical studies of Dr Julius led to the discovery that TRPV1functions as heat-sensing (33-38°C) receptor also. This is activated at temperatures perceived as painful and thus plays a role tosense noxious heat in humans. It is a breakthrough to understand how even small differences in temperature can induce electrical signals in the nervous system. In 1997, this opened a nascent field in the quest to understand the molecular and neural basis for thermal sensing.

The structure of TRPV1 at near-atomic scale was reported in 2013 by Juliusand his UCSF colleague Yifan Cheng using cryo-electron microscopy. This helps in design of new drugs for critical pain relieving.

Sensing of warmth in humans and mice: TRPV1 was initially deemed as a noxious heat receptor. But later studies unexpectedly revealed that it significantly contributes in detection of innocuous warmth. This protein also contributes to the hypersensitivity to heat felt in injured tissue, such as sunburned skin, where evenmild stimuli can be perceived by the brain as burning hot.

Research with noxious substances: Julius carried out extensive deep level research of noxious substances including toxins from tarantulas and coral snakes, chemicals underlying the pungency of horseradish wasabi,capsaicin etc. This is in order to understand how signals responsible for temperature and pain sensation are transmitted by neural circuits to the brain paving way for exploring new trends in drugs to mitigate diseases cropping by gene mutations.

Deletion of corresponding gene for activation of this channel in mice produced deficiencyin the sensation of innocuous warm temperatures in the range of 33-38°C.

TRPA1: In 2015, Julius and Cheng used cryo-Electron Microscopy to determine the structure of TRPA1, the "wasabi receptor." It responds to the pungent compounds in wasabi and is also involved in inflammatory pain.

TRPM2: Peter McNaughton's group identified another TRP channel, TRPM2, as a potential warmth sensor.

TRPM8: The receptor, TRPM8receptor responds to either cool temperatures or menthol.

In totality, the emerging picture is that TRPV1, TRPA1, TRPM2 and TRPM3 ion channels collectively act as warm sensors with adequate experimental evidence. One more condition to be satisfied is thatwarmth sensation is reliably signalled only when the activity in TRPM8 containing cold-sensing nerve fibers is simultaneously suppressed by warm temperatures. With experimental evidences for valid knowledge of sensation of cold, warmth and Capsaicin hot taste, additional bits of information will fill the gaps in this known for long (centuries)-yet not-known-completely till-now area of human medical/pathogenic physiology.

Cold (Thermal energy T <) Sensation in humans: The non-noxious cold sensation in humans starts at around 28°C. The detection of even a small change in skin temperature (0.5°C) is remarkable. In 2002, another ion channel TRPM8, another member of TRP super family, was discovered independently in laboratories of Julius and Patapoutian for cold-sensation. This knowledge emerged as a consequence of functional screens based on menthol, a natural compound that elicits the sensation of innocuous coolness in humans. The compound binds ion channel activated by cold (temperature) stimulus.

TRPM8: Julius, Patapoutian and other groups independently found that deletion of Trpm8 in mice causes clear deficits in sensation of innocuous cold.
Additional ion channels related to TRPV1 and TRPM8 were identified and found to be activated by a range of different temperatures.

Ardem Patapoutianera [6-8]: Ardem Patapoutian at Scripps Research Laboratory together with Bertrand Coste (postdoctoral research scholar) screened several mouse and rat cell lines by applying force (pressure) on the Neuro2A cell surface with a piezo-electrically driven glass probe. Another pipette was used in patch-clamp recording in the whole cell configuration. Neuro2A (N2A) mouse neuroblastoma cell line expressed the MA currents most consistently. With the identification of this mechanosensitive Neuro2A cell line, they carried out global expression analysis. It was found that 72 candidate genes predicted to encode proteins with at least two membrane-spanning domains, which included known ion channels and proteins of unknown function.

Affiliation at the time of the award	Nobel Laureate (Med) Photo Date & place of birth	Share

Howard Hughes Medical Institute, Scripps Research, La Jolla, CA, USA	Ardem Patapoutian  Born: 1967, Beirut, Lebanon	½

https://www.nobelprize.org/prizes/medicine/2021/patapoutian/facts
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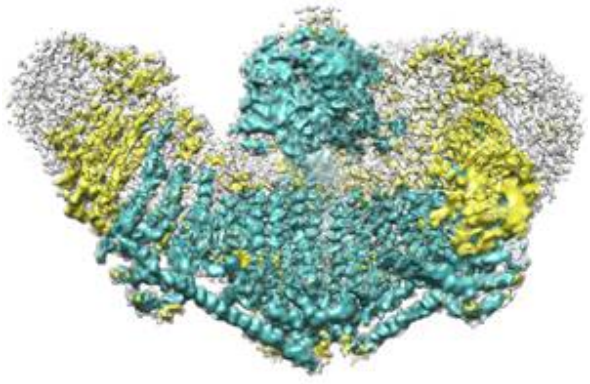
The analysis was repeated by silencing this set of genes one-by-one by-RNA-interference. The knocking of final, 72nd gene (earlier known as FAM38A) rendered the cells insensitive to poking with the micropipettei.e., there was no mechanically activated current. PIEZO1 was the name given to this protein as well as gene; "piesi" meaning pressure in Greek language.

PIEZO proteins: They belong to largest transmembrane ion channel subunits previously unknown protein family present in vertebrates and many other eukaryotes. These proteins have 2,500 amino acids and display a unique 38 transmembrane helix topology. Their function in vertebrates is as mechano sensitive channels [**9-13**].

PIEZO1Gene: This gene exercises a key role to sense mechanical forces in endothelial and redblood cells.

In mice the mechanical load-dependent bone formation relies on PIEZO1.



Side view of PIEZO1 ion channel

PIEZO2Gene: Through the similarity in expression and function to Piezo1, Patapoutian discovered a second gene employing sequence homology and called it Piezo2. Sensory neurons were found to express high levels of Piezo2 and its structure was elucidated. Further research unravelledthe function of PIEZO2 as the major mechanical transducer in somatic nerves and is required for our perception of touch (hug)and proprioception. It isabilityto sense/feel the position and motion/movement of our body parts.PIEZO2, but not PIEZO1, was found to be expressed in dorsal root ganglion sensory neurons. Itsknockdown abolishes the mechano-sensitivity of these sensory neurons. This gene regulates othercritical physiological processes viz. blood pressure, respiration and urinary bladder control.

These channels present on pulmonary stretch receptors in the wall of bronchi. The bronchioles are activated by large inspirations and initiate a reflex protecting the lung from over-inflation.

Consequences of mutations, loss of function of PIEZO2: Loss-of-function mutations in the PIEZO2 gene result in multiple disorders. In distal arthrogryposis (D), the manifestation is congenital contractions in multiple joints of fingers, feet/toes,severely uncoordinated body movements and abnormal limb positions. In other distress, adult humans display profound deficiency in touch sensation, including texture discrimination, hair deflection as well as tactile and vibration sensitivity.

The high-resolution structure of PIEZO1 and PIEZO2 reported by Patapoutian and others showed that these channels form homotrimeric structures with a central ion-conducting pore and three peripheral large mechanosensing propeller-shaped blades. They are directly activated by the exertion of pressure on cell membranes. Mice lacking Piezo1 and Piezo2 display a labile hypertension and have increased blood pressure variability. The direct evidence for light touch sensitivity comes from experiments of Patapoutian and other researchers in 2014, which showed that Merkel cells display a PIEZO2-dependent current evoked by fast touch.

REFERENCES

[1]. https://www.nobelprize.org/prizes/medicine/**1906**/summary/
[2]. https://www.nobelprize.org/prizes/medicine/**2021**/press-release/
2021-10-04, Press release: The Nobel Prize in Physiology or Medicine, **2021**
[3]. Fischer MJM, Ciotu CI and Szallasi A,The Mysteries of Capsaicin-Sensitive Afferents, *Front. Physiol*., **2020**, 11, 554195.doi: 10.3389/fphys.2020.554195.
[4]. Y. M. Shuba, Beyond Neuronal Heat Sensing: Diversity of TRPV1 Heat-Capsaicin Receptor-Channel Functions, Front, Cell. *Neurosci.,* **2021**, 14, Article 612480.
doi: 10.3389/fncel.2020.612480
[5]. Michael J. Caterina, Mark A. Schumacher, Makoto Tominaga, Tobias A. Rosen, Jon D. Levine and David Julius The capsaicin receptor: a heat-activated ion channel in the pain pathway *Nature*, **1997**, 389, 816-824.
[6]. Shang Ma, Adrienne E. Dubin, Yunxiao Zhang, Seyed Ali Reza Mousavi, Yu Wang, Adam M. Coombs, Meaghan Loud, Immacolata Andolfo, and Ardem Patapoutian1,A role of PIEZO1 in iron metabolism in mice and humans,*Cell* , 184, 969–982, February 18, 2021,
doi.org/ 10.1016/ j.cell.2021.01.024.
[7]. Bertrand Coste, Jayanti Mathur, Manuela Schmidt, Taryn J. Earley1, Sanjeev Ranade, Matt J. Petrus, Adrienne E. Dubin, and Ardem Patapoutian,Piezo1 and Piezo2 are essential components of distinct mechanically-activated cation channels, *Science*., **2010**, 330(6000), 55–60.
doi:10.1126/science.1193270.
[8]. L. Kara, Marshall, Dimah Saade, Nima Ghitani, Adam M. Coombs, Marcin Szczot, Jason Keller, Tracy Ogata, Ihab Daou, Lisa T. Stowers, Carsten G. Bönnemann, Alexander T. Chesler andArdem Patapoutian1, PIEZO2 in sensory neurons and urothelial cells coordinates urination, *Nature*, **2020**, 588, 290–295, doi.org/10.1038/s41586-020-2830-7.
[9]. Douguet D and HonoréE, Mammalian mechanoelectrical transduction: structure and function of force-gated ion channels, Cell, 2019, 179, 340–354.
[10]. Jin P, Jan LY and Jan Y-N,Mechanosensitive ion channels: structural features relevant to mechanotransduction mechanisms, *Annu. Rev. Neurosci*., **2020**, 43, 207–229.
[11]. Ajay Dhaka,Veena Viswanath, Ardem Patapoutian, TRP Ion Channels andTemperature Sensation, *Annu. Rev. Neurosci*., **2006**, 29, 135–61
[12]. Lu Gao, Yun Ji, Lulu Wang, Meixia He, Xiaojing Yang, Yibing Qiu, Xu Sun, Zhenyu Ji, Guanrui

Yang,Jianying Zhang, Shanshan Li, Liping Dai, and Liguo Zhang, Suppression of Esophageal Squamous Cell Carcinoma Developmentby Mechanosensitive Protein Piezo1 Downregulation, *ACS Omega*, 2021, 6, 0196−10206.

[13]. Nicholas W. Bellono, James R. Bayrer, Duncan B. Leitch, Joel Castro, Chuchu Zhang, Tracey A. O'Donnell,Stuart M. Brierley, Holly A. Ingraham, and DavidJulius,Enterochromaffin Cells Are Gut Chemosensorsthat Couple to Sensory Neural Pathways, Cell 2017, 170, 185-198doi.org/10.1016/j.cell.2017.05.034.