Why Indian Scientific Contributions do not Fetch Nobel Prize

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On 4th October 2021, the announcement came that David Julius, along with Ardem Patapoutian, bagged the Nobel Prize in medicine for this year for their work on capsaicin receptors in the skin that sense temperature and touch [1]. Main headline of one national newspaper on 5th October was “Indian lab may have helped validate research that fetched the medicine Nobel.” It stated that The Indian Institute of Chemical Biology (IICB) under the CSIR had shown in 2018 that the cells of the immune system may also be critically dependent on these capsaicin channels to sense the physical cues they encounter inside the body [2]. The scientific community, journals, administrators, and politicians need to look critically at such claims and counterclaims for introspection and futuristic measures. As *Sleep and Vigilance* is a sleep-related journal, we are taking some sleep-related contributions from India on the subject of capsaicin for which the Nobel Prize in medicine for 2021 was awarded. Julius told *Scientific American* in 2019 that he got the idea to study chili peppers after a trip to the grocery store. “I was looking at these shelves and shelves of basically chili peppers and extracts (hot sauce) and thinking, ‘This is such an important and such a fun problem to look at. I’ve really got to get serious about this’,” he said [3].

According to a statement by the Nobel Assembly, David Julius utilized capsaicin, a pungent compound from chili peppers that induces a burning sensation, to identify a sensor in the nerve endings of the skin that responds to heat. Ardem Patapoutian identified two mechanically activated ion channels, named Piezo1 and Piezo2. He uncovered the central roles of Piezo1 and Piezo2 for many additional physiological

functions. The work by the two laureates has unlocked one of the secrets of nature by explaining the molecular basis for sensing heat, cold, and mechanical force, which are fundamental for our ability to feel, interpret and interact with our internal and external environments.

The national newspaper stated that a scientific paper titled “Cutting Edge: Piezo1 Mechanosensors Optimize Human T Cell Activation”, published by IICB scientists in *The Journal of Immunology* provided evidence for the involvement of Piezo mechanosensors in immune regulation [4]. Their contribution to one of the two mechanically-activated ion channels, i.e. Piezo1, identified by Ardem Patapoutian is certainly worth admiring.

The first paper of David Julius, which has a reference to capsaicin, was published in a nine-author paper, in the *Proceedings of the National Academy of Sciences*, on 23rd Aug 2005, where he was the 7th author. Based on their research on tissues collected from rats, they conclude: “Here we show that allicin and diallyl disulfide (DADS) excite an allyl isothiocyanate-sensitive subpopulation of sensory neurons and induce vasodilation by activating capsaicin-sensitive perivascular sensory nerve endings.” They have studied the molecular mechanisms underlying the action of allicin and DADS [5]. But they have not studied any systemic physiological responses, at least in this paper. Even induced vasodilation is an assumption based on the estimation of the release of calcitonin gene-related peptide (CGRP). This is not to underestimate the importance of their contribution, which is rightly recognized by the Nobel Prize.

It is possible to make breakthroughs in molecular investigations and then follow up with systemic physiological studies. Alternatively, discoveries can be made by systemic physiological investigations, and subsequently, molecular mechanisms involved in the process can be investigated. Scientific thinking has changed over the last few decades, which will be discussed towards the end of this write-up. Rightly or wrongly, it is the first pathway in research that is given importance and recognition by science administrators and scientific journals.

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Here we would like to take the example of one study which followed the second pathway. The functional importance of capsaicin receptors in sleep was demonstrated by a group of scientists from the *All India Institute of Medical Sciences* (AIIMS), New Delhi. Their publication in the journal *Physiology & Behavior* appeared in print on 21st Jul 2005, which is a month earlier than the above-mentioned publication of David Julius. “Ambient temperature related sleep changes in rats neonatally treated with capsaicin” was the title of the article by Gulia KK, Mallick HN, and Kumar VM from India [6]. Their results showed that the central warm receptors can produce alteration in sleep, even in the absence of peripheral warm receptors. This is a piece of important information for the understanding of the ion channels activated by capsaicin.

The group led by Hruda Nanda Mallick from the Department of Physiology, AIIMS, continued their studies on central capsaicin receptors and they published in 2011, their paper titled “Warm sensitive neurons of the preoptic area regulate ambient temperature related changes in sleep in the rat” in *Indian Journal of Physiology and Pharmacology* [7]. Their study showed that warm sensitive neurons play a major role not only in thermoregulation but also in sleep regulation. They studied changes in sleep and body temperature in rats before and after the destruction of warm sensitive neurons (WSN) of the preoptic area (POA) by local intracerebral injection of capsaicin. It showed that the REM sleep generation is under inhibitory control of the WSN of the POA. In another paper titled “Ambient temperature-dependent thermoregulatory role of REM sleep” published in 2012 in the *Journal of Thermal Biology*, they studied thermoregulation and sleep after the destruction of both peripheral and central warm receptors, by systemic administration of capsaicin [8]. Results of this study showed that the ambient temperature-related increase in REM sleep at higher atmospheric temperature could be part of the thermoregulatory measures. Another paper titled “Participation of preoptic area TRPV4 ion channel in regulation of body temperature” published by them in the *Journal of Thermal Biology* in 2017 identified the channels activated by capsaicin [9]. The results of this study suggested that TRPV4 ion channels in the POA play an important role in thermoregulation.

1 What ails Indian Science?

There are a variety of reasons why Indian scientists’ contributions are overlooked. Even though the Indian government has launched various programmes to encourage young people to pursue scientific research, there are only a few takers. Professional courses are preferred by the majority of students. Administrative services have a high level of appeal among them. Though the girls are dedicated to their

work, and there are some outstanding female scientists, there is a prevailing perception, particularly in the field of sleep research, that this is a man’s world, due to its demand for long periods of work at unusual hours.

In India, the majority of research is funded by governmental agencies. These financing agencies’ operations are far from admirable. They spend months, if not years, assessing the projects that they receive. Even after ‘experts’ have evaluated the proposals, another panel meets to decide who should receive financing. Those who are fortunate enough to receive the expert group’s endorsement will have to wait eternally for funding to be granted for study. Only individuals working in educational and scientific institutions are eligible for funds. The money does not go directly to the researcher; instead, it goes to the institution where the scientists are employed. The institute is responsible for ensuring that the funds are used for the purpose for which they were provided. It is a very good administrative method, but scientists must be on good terms with the lower administrative staff to ensure that the latter do not put hurdles in the appointment of research staff and the utilization of funds.

Though India has a large number of science graduates, the people who do good research are extremely few. The number of educational institutions doing any kind of research is also low. Basic research does not get sufficient support in India, though it is true that basic research is not a priority all over the world. Governments have been obliged to reduce budget allocations for research in general due to fiscal constraints, yet everyone understands that science cannot progress without the contribution of basic research.

Furthermore, Europe and North America have a monopoly on scientific publications, particularly in the field of medicine. In most cases, Indian manuscripts are not endorsed for publication. Unfortunately, a high rate of rejection is often used as a gauge of a journal’s scientific credibility. Journals boast about their high rejection rate to project their standing in the scientific world. Despite the fact that they claim to encourage contributions from all across the world, the articles are rejected at the editorial level, even before they are peer-reviewed. Even when there are no negative criticisms, many manuscripts are rejected on some lame excuse.

Many journals set a limit on the number of references that can be included in a single publication. This encourages people to look at the publications of people who might be evaluating their articles. Many journals have begun to charge exorbitant fees for publishing. Even governmental entities find it difficult to sponsor the publications since the costs are so high. Some top-ranking journals have started the policy of considering for publication only papers from those individuals who have been asked to submit their works.

International politics has also made an appearance in scientific journals. Medical publications are typically trusted, and their viewpoints are seen as gospel truth, in contrast

to general media stories, which are taken with a grain of salt. Leading medical publications have risen to the status of “superpowers”. Many of these journals offer provisions for including articles that discuss government health policies. They are blatantly abused to serve some countries’ economic and political objectives. Many political decisions are based on studies published in these elite medical publications, which the general public holds in high regard and confidence. Many countries, as well as so-called charity trusts, have begun to fund a number of influential medical journals.

One very encouraging thing that has happened in scientific thinking is the emphasis that is given to molecular studies. But unfortunately, systemic physiological research that ultimately gives the validation (i.e. applicability of the studies) in a living system, has been pushed into oblivion. The journalists of the leading Indian newspaper (mentioned earlier) could find only a 2018 publication in the molecular/biochemical field which stated that an Indian lab may have helped validate research that fetched the Nobel Prize in medicine. This is not to belittle the importance of the studies of IICB scientists. Even the journalists cannot think beyond the popular perception that molecular/biochemical research is the only meaningful research.

The discovery of physiological changes during paradoxical sleep (or REM sleep) is widely regarded as one of the most significant breakthroughs in not only sleep science but also neuroscience and medical science. However, it remains a mystery why none of those engaged in the discovery were awarded the Nobel Prize. The “paradoxical stage” or “phase” of sleep was first defined in 1959 by Michel Jouvét, a neurosurgeon turned neurophysiologist. During this stage of sleep, neo-decorticated cats showed periodic loss of tonic neck-muscle activity, the presence of nictitating membranes covering the strong myotic eyes, and small vibrissae movements [10]. Jouvét had devoted his entire professional career to furthering this field of science. Even he had trouble finding funding for his research. If he desired big research funding, the funding agency urged him to submit proposals related to molecular biological investigations. This is akin to asking an elephant to fly to demonstrate its strength.

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