Classic paper

Presented by: Riya Dutta

28-12-2024

Article | Published: 23 October 1997

The capsaicin receptor: a heat-activated ion channel in the pain pathway

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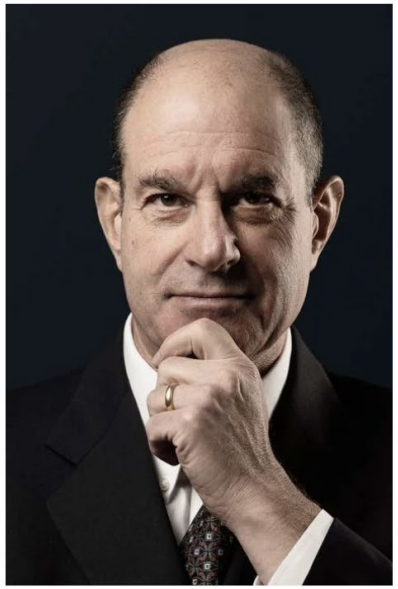
Nature **389**, 816–824 (1997) | Cite this article

The Nobel Prize in Physiology or Medicine 2021



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David Julius

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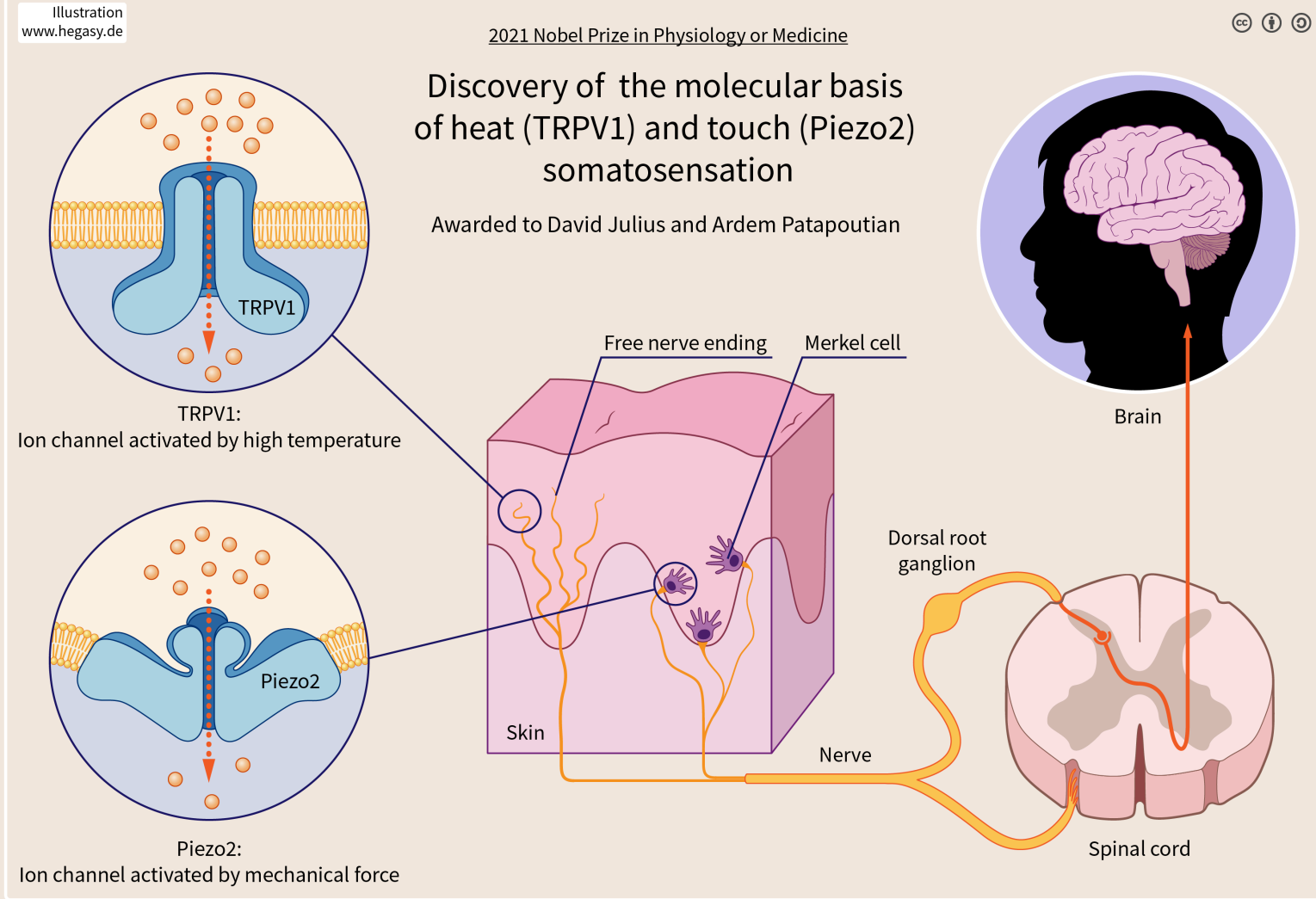
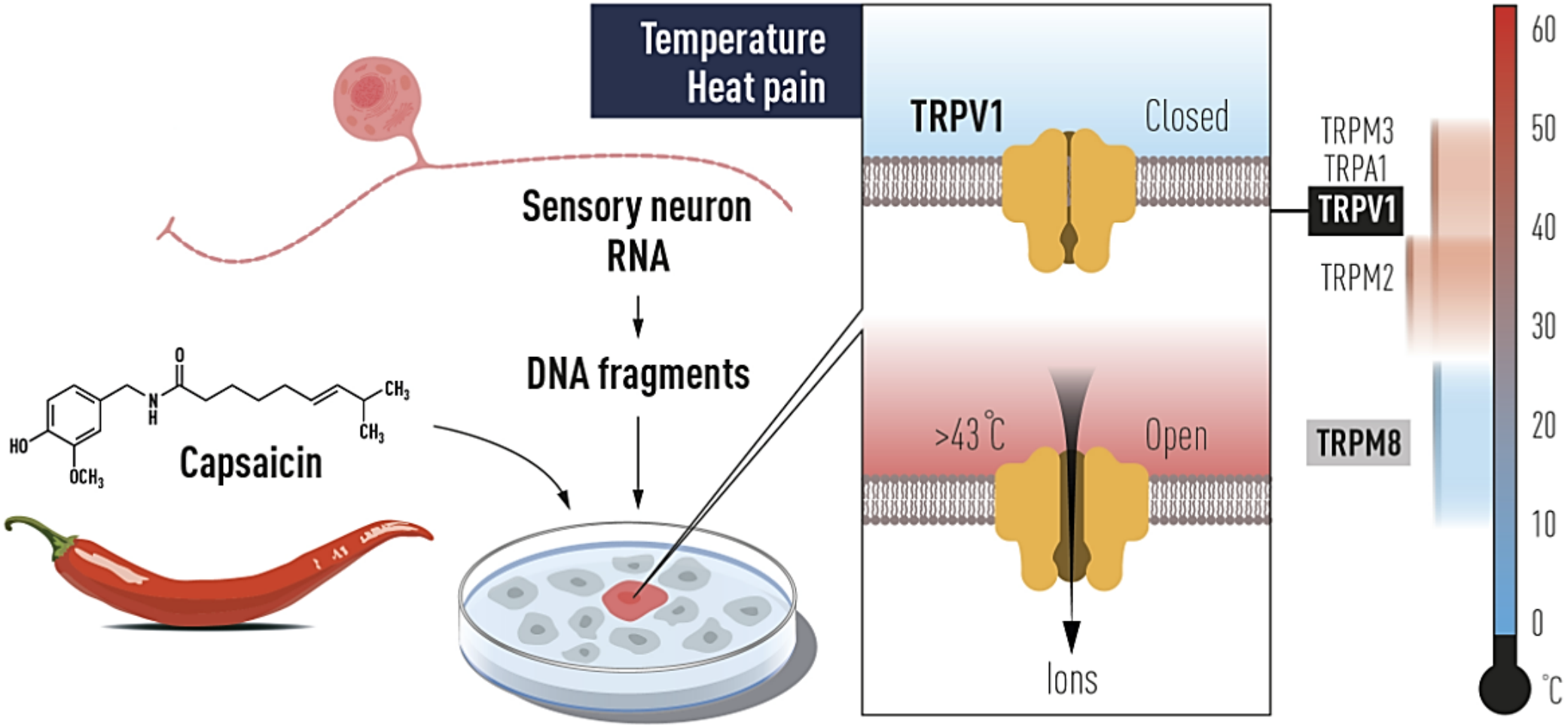


The capsaicin receptor: a heat-activated ion channel in the pain pathway

Access & Citations

Online attention

Background


Temperature
Heat pain
Sensory neuron
RNA
DNA fragments
Capsaicin
HO
OCH3
N
H
O
CH3
CH3
TRPV1
Closed
>43°C
Open
Ions
TRPM3
TRPA1
TRPV1
TRPM2
TRPM8
60
50
40
30
20
10
0
°C

Abstract

Capsaicin, the main pungent ingredient in 'hot' chilli peppers, elicits a sensation of burning pain by selectively activating sensory neurons that convey information about noxious stimuli to the central nervous system. We have used an expression cloning strategy based on calcium influx to isolate a functional cDNA encoding a capsaicin receptor from sensory neurons. This receptor is a non-selective cation channel that is structurally related to members of the TRP family of ion channels. The cloned capsaicin receptor is also activated by increases in temperature in the noxious range, suggesting that it functions as a transducer of painful thermal stimuli *in vivo*.

Pain is initiated when the peripheral terminals of a subgroup of sensory neurons are activated by noxious chemical, mechanical or thermal stimuli. These neurons, called nociceptors, transmit information regarding tissue damage to pain-processing centres in the spinal cord and brain[1]. Nociceptors are characterized, in part, by their sensitivity to capsaicin, a natural product of capsicum peppers that is the active ingredient of many 'hot' and spicy foods. In mammals, exposure of nociceptor terminals to capsaicin leads initially to excitation of the neuron and the consequent perception of pain and local release of inflammatory mediators. With prolonged exposure, nociceptor terminals become insensitive to capsaicin, as well as to other noxious stimuli[2]. This latter phenomenon of nociceptor desensitization underlies the seemingly paradoxical use of capsaicin as an analgesic agent in the treatment of painful disorders ranging from viral and diabetic neuropathies to rheumatoid arthritis[3,4]. Some of this decreased sensitivity to noxious stimuli may result from reversible changes in the nociceptor, but the long-term loss of responsiveness can be explained by death of the nociceptor or destruction of its peripheral terminals following exposure to capsaicin[2,5].

Although the excitatory and neurotoxic properties of capsaicin have been used extensively to define and study nociceptive neurons, its precise mechanism of action has remained elusive.

A more detailed understanding of the molecular nature of capsaicin action and its relationship to endogenous pain signalling mechanisms might be obtained through the cloning of a gene encoding a capsaicin receptor.

Expression cloning of receptor cDNA

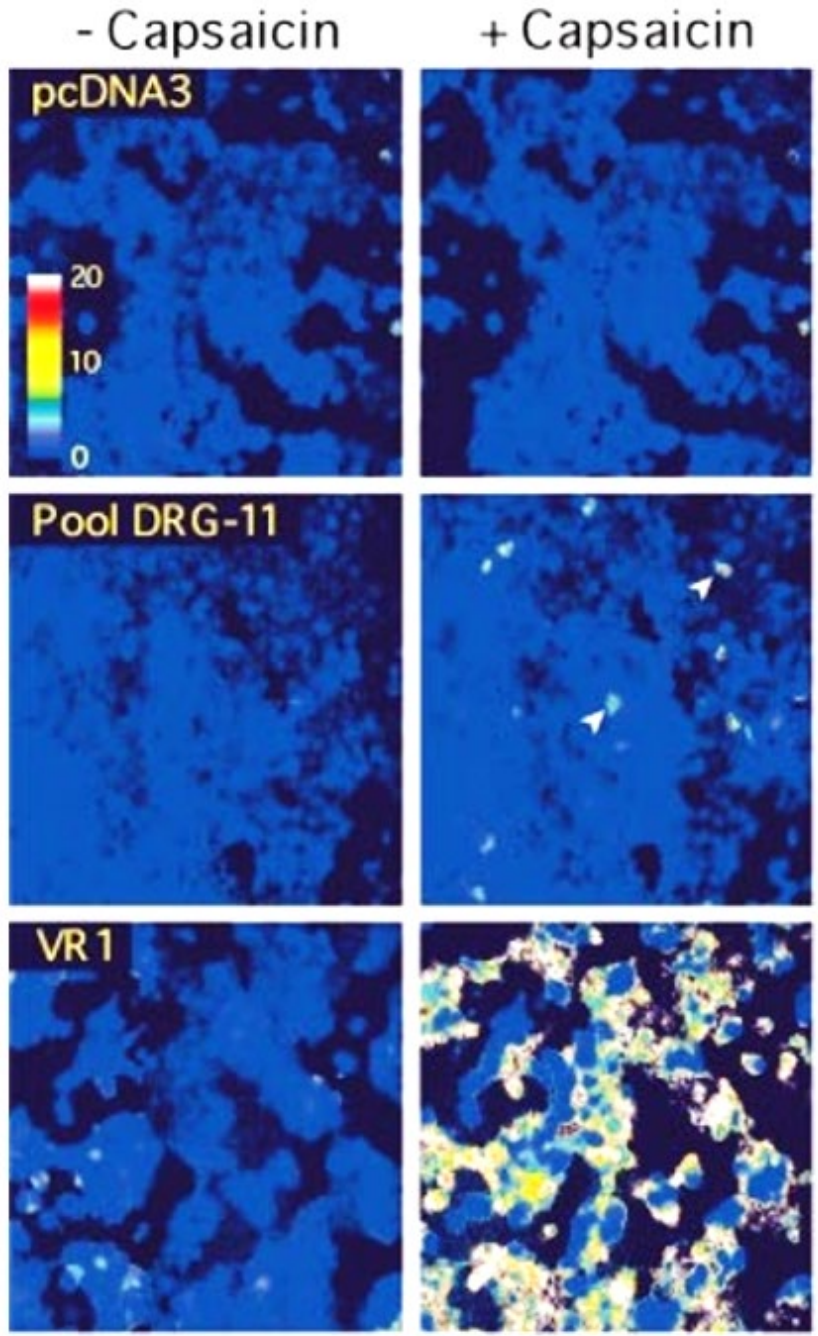
The lack of specific information regarding the molecular structure of capsaicin receptors prompted us to adopt a functional screening strategy for isolating candidate cDNA clones.

expression cloning strategy was devised on the basis of the ability of capsaicin to trigger robust calcium influx into sensory neurons *in vitro*[9,17].

cDNA library was constructed from dorsal root ganglion-derived messenger RNA. This library was subdivided into pools of approximately 16,000 clones, and each pool was transiently transfected into human embryonic kidney-derived HEK293 cells. Transfected cells were then loaded with the fluorescent calcium-sensitive dye Fura-2

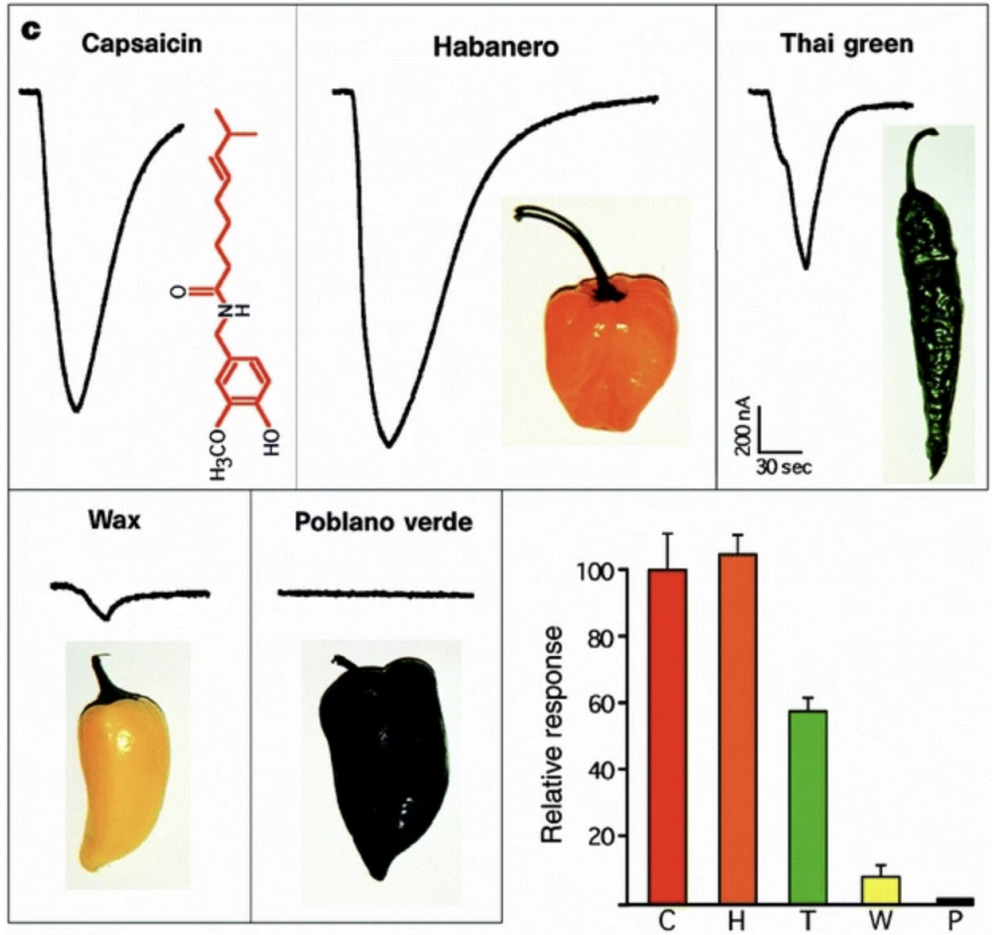
changes in intracellular calcium levels. A positive pool was identified (Fig. 1, middle) and iteratively subdivided and reassayed. In this way, an individual clone containing a 3-kilobase (kb) cDNA insert was obtained that, by itself, conferred capsaicin (Fig. 1, bottom)

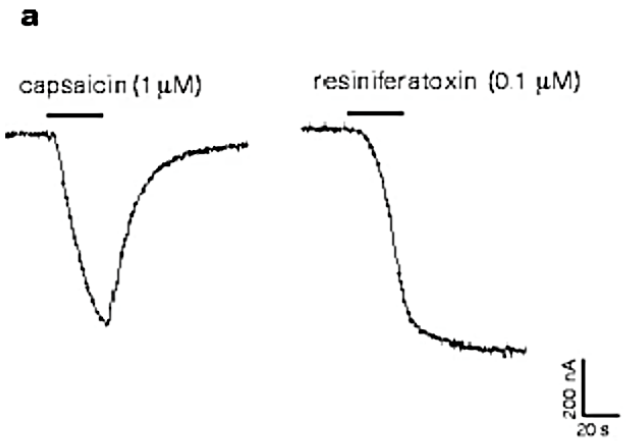
Because a vanilloid moiety constitutes an essential chemical component of capsaicin and resiniferatoxin structures, the proposed site of action of these compounds is more generally referred to as the vanilloid receptor[16]. Accordingly, we have named the newly cloned cDNA VR1, for vanilloid receptor subtype 1.

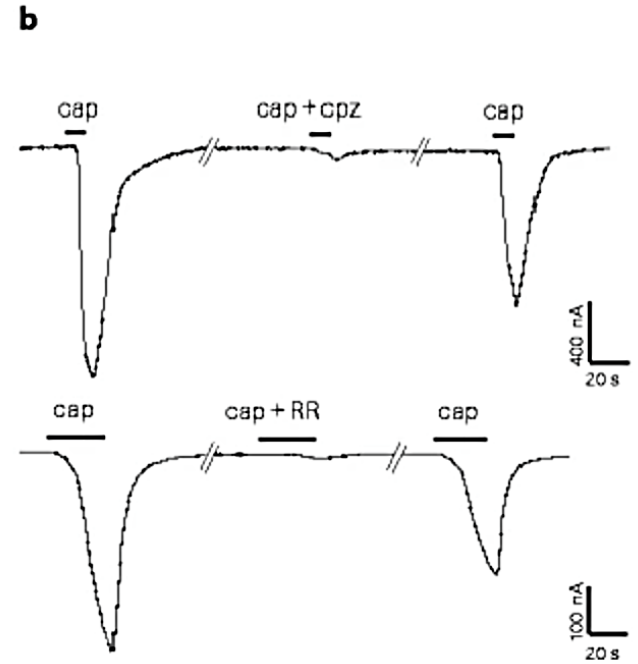


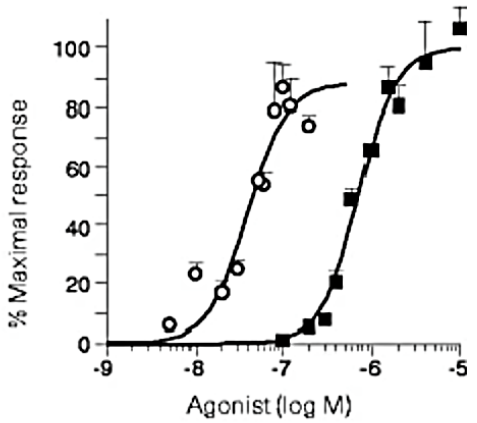
VR1 and vanilloid receptor pharmacology

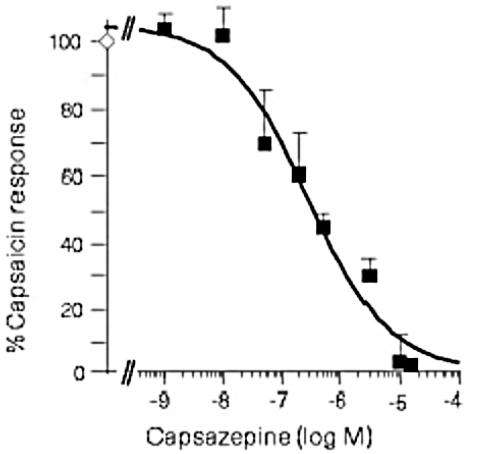
To compare the pharmacological properties of th
to those of native vanilloid sites in sensory gang
VR1 in *Xenopus* oocytes and used whole-cell volta
to quantitatively examine the electrophysiologic
variety of vanilloid agonists and antagonists. At











ms

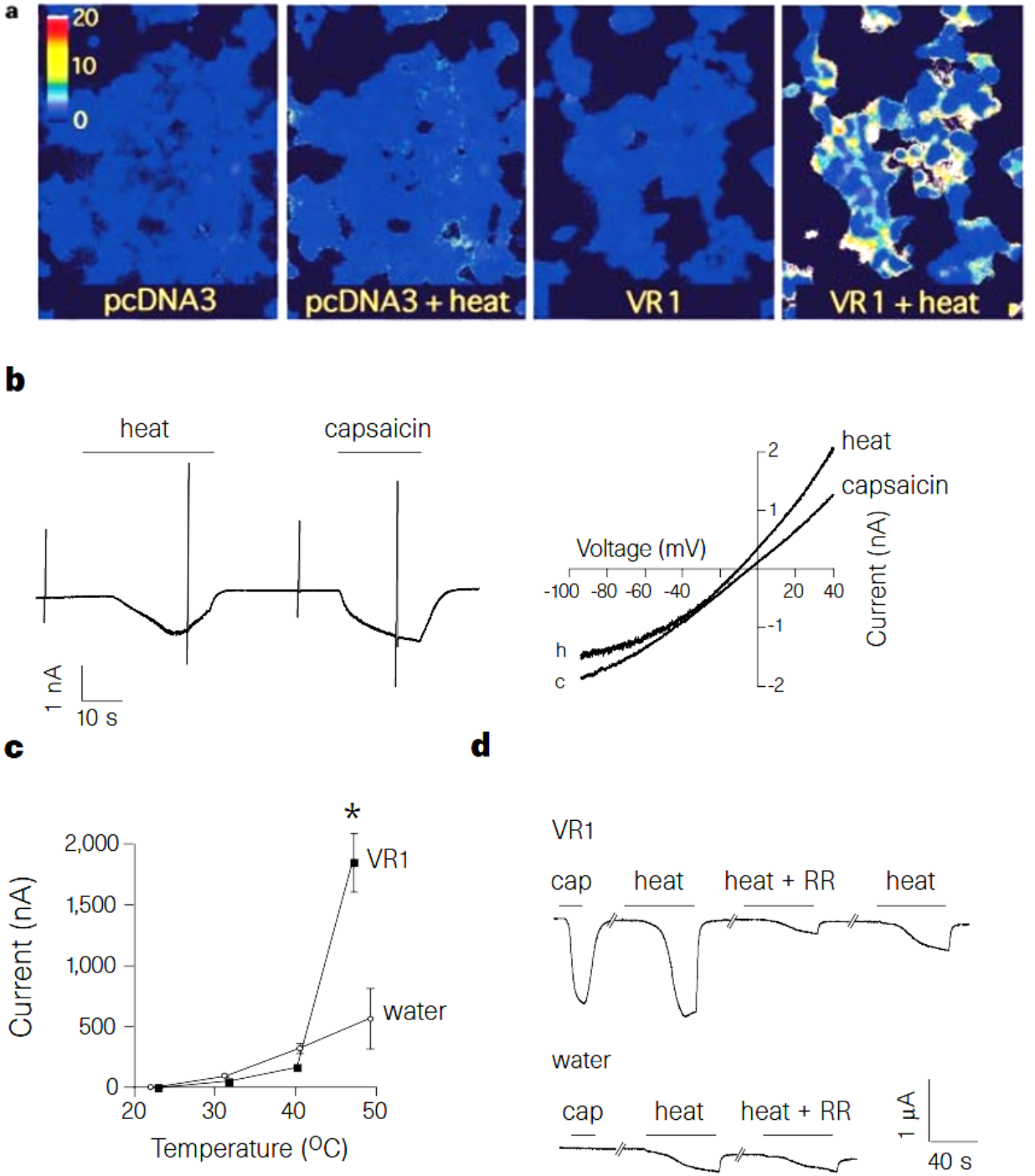
CPZ = CPZ stands for **"capsazepine"** a blocker that prevents capsaicin from working.
RR = RR refers to **"ruthenium red"** a blocker that prevents capsaicin from working.

Vanilloid receptor activated by noxious heat

The 'burning' quality of vanilloid-induced pain suggests that vanilloids and heat may evoke painful responses through a common molecular pathway. We therefore explored the effects of elevated temperature on VR1 activity. In initial studies, transfected HEK293 cells were subjected to fluorescent calcium imaging

a sudden increase in ambient temperature from 22 °C to ~45 °C. Under these conditions, cells transfected with vector alone exhibited only a mild, diffuse change in cytoplasmic free calcium (Fig. 7a, left). In contrast, a large proportion of cells expressing VR1 exhibited a pronounced increase in calcium levels within seconds of heat treatment (Fig. 7a, right).

examined using patch-clamp methods. Exposure of these cells to a rapid increase in temperature (22 °C to ~48 °C in 25 s, monitored using an in-bath thermistor) produced large inward currents (791 ± 235 pA at −60 mV, $n = 9$) that were typically similar in amplitude to that evoked by a subsequent application of capsaicin at 500 nM (Fig. 7b). Both heat- and vanilloid-evoked responses showed outward rectification, suggesting that they are mediated by the same entity (Fig. 7b).



David Julius

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Spouse	Holly Ingraham
Awards	Nobel Prize for Medicine (2021) Breakthrough Prize in Life Sciences (2020)

Scientific career

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Doctoral advisor	Jeremy Thorner Randy Schekman

Thank You