PERSPECTIVES

A direct demonstration of functional TRPV1 in Cajal–Retzius cells

Roger J. Thompson
Hotchkiss Brain Institute, Department of Cell Biology and Anatomy, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
Email: rj.thompson@ucalgary.ca

Edited by: Jaideep Bains & Katalin Toth

The transient receptor potential vanilloid 1 (TRPV1) channel is responsible for detecting noxious heat and the 'spicy' (i.e. capsaicin) sensation. These highly Ca^{2+}-permeable non-selective cation channels are gated by pH and endovanilloids such as anandamide (AEA). TRPV1 functional responses in the brain have been reported by several groups using a diversity of techniques ranging from immunohistochemistry to knockout animals and pharmacological effects on plasticity. For example, Gibson *et al.* (2008) reported immunohistochemical expression of TRPV1 in hippocampus and functional effects of the channel's agonists (i.e. capsaicin) and antagonists (i.e. capsazapine) on long-term depression at excitatory synapses onto interneurons (Gibson *et al.* 2008). In contrast, Cavanaugh *et al.* (2011) detected no TRPV1 in hippocampal pyramidal neurons of a reporter mouse line. They also failed to find capsaicin-induced changes in Ca^{2+} (Cavanaugh *et al.* 2011). This has sparked controversy surrounding the functional presence of TRPV1 in the hippocampus.

Other groups have shown that postsynaptic TRPV1 in dentate granule cells can induce an LTD-like response when activated by AEA (Chávez *et al.* 2010). The same group (Castillo) also later reported a compartmentally specific role for TRPV1 in AEA-mediated suppression of somatic GABA responses. Despite these convincing papers, they all failed to show *direct* TRPV1 ion currents or changes in intracellular Ca^{2+}, providing critics with a solid foundation to doubt the presence of TRPV1 because alternative channels, such as TRPV4, could be involved. The only way to assuage these criticisms would be the direct demonstration of TRPV1 currents and functional responses in the hippocampus.

In this issue of *The Journal of Physiology*, Anstötz and colleagues report that Cajal–Retzius (CR) cells in the hippocampus express functional TRPV1 channels that have a role in the activation of GABAergic interneurons in the molecular layer (Anstötz *et al.* 2018) It is interesting to note that the CR cells were the only hippocampal cell type reported by Cavanaugh *et al.* to express TRPV1. It has been known since the 1990s that CR cells innervate the several regions of the hippocampal formation, including the cornu Ammonis (CA) and dentate gyrus (Anstötz *et al.* 2016). In the present work, Anstötz and colleagues have built on this anatomical description to demonstrate active and functional TRPV1 channels.

Central to their ability to probe the potential functional expression of TRPV1 in CR cells was the generation of reporter mice and TRPV1 knockouts. They first showed robust increases in intracellular Ca^{2+} in response to the TRPV1 agonist capsaicin in identified CR cells using slices from the Wnt3a-GCaMP6s mouse line. This confirmed that these capsaicin-induced increases in Ca^{2+} did not require network activity, making this, to the best of my knowledge, the first demonstration of direct TRPV1-mediated Ca^{2+} changes in hippocampal cells. Further confirmation of active plasmalemma TRPV1 was obtained with Ca^{2+} imaging in nominally Ca^{2+} free extracellular solutions and in voltage-clamp, where capsaicin-induced inward currents (at −60 mV) were recorded in acute slices from CXCR4-EGFP or Wnt3a-tdTomato mice. As expected, capsaicin-activated currents were absent in the CXCR4-EGFP TRPV1$^{-/-}$ mice. While it would have been interesting to see the entire current–voltage relationship of CR TRPV1 (a task that is possible in these high-input resistance cells), the data show a convincing role for these enigmatic channels in hippocampal cells. A further interesting observation was that TRPV1 was detected only in about half of the CR cells evaluated. The reason for this is unclear, but the authors suggest two possibilities: that only half of CRs express TRPV1 or that in that population TRPV1 is inactivated by an as yet unidentified mechanism. A TRPV1-Cre line could help address this issue.

So what might CR TRPV1 be doing? Considering that CR cells likely innervate both the dentate gyrus and CA layers, the authors postulated that CR TRPV1 may be involved in local hippocampal microcircuits. They focused on the effects of capsaicin on GABAergic interneurons of the molecular layers. Voltage-clamped interneurons from the CXCR4-EGFP TRPV1$^{+/+}$ but not CXCR4-EGFP TRPV1$^{-/-}$ mice showed a dramatic increase in spontaneous glutamatergic EPSCs by capsaicin. A comparison of TRPV1 activation on molecular layer *versus* stratum oriens interneurons revealed a much more dramatic increase in sEPSC frequency in the former. This was supported by anatomical reconstructions to ensure the location of the interneurons.

In summary, the demonstration by Anstötz *et al.* that CR neurons have functional TRPV1 channels that can influence synaptic transmission in the molecular layers of the hippocampus has interesting implications for physiology and pathology. The Ca^{2+} permeability of TRPV1 suggests that the channel in synaptic boutons could regulate neurotransmitter release, which is supported by Anstötz *et al.*'s work. It will be of interest to determine if CR synapses onto pyramidal neurons show a similar enhancement of sEPSC activity upon TRPV1 opening. Although not addressed in the current work, understanding the endogenous activation of TRPV1 in the hippocampus (i.e. without capsaicin application) is an important future goal to truly appreciate the physiological functions of these channels. Some possibilities include regulation of TRPV1 by AEA, as has been proposed in the dentate gyrus (Chávez *et al.* 2010), or by temperature, which could be an important mediator of febrile seizures.

References

Anstötz M, Huang H, Marchionni I, Haumann I, Maccaferri G & Lübke JHR (2016). Developmental profile, morphology, and synaptic connectivity of Cajal–Retzius cells in the postnatal mouse hippocampus. *Cereb Cortex* **26**, 855–872.

Anstötz M, Lee SK & Maccaferri G (2018). Expression of TRPV1 channels by Cajal-Retzius cells and layer-specific modulation of synaptic transmission by capsaicin in the mouse hippocampus. *J Physiol* **596**, 3739–3758.

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Cavanaugh DJ, Chesler AT, Jackson AC, Sigal YM, Yamanaka H, Grant R, O'Donnell D, Nicoll RA, Shah NM, Julius D & Basbaum AI (2011). Trpv1 reporter mice reveal highly restricted brain distribution and functional expression in arteriolar smooth muscle cells. *J Neurosci* **31**, 5067–5077.

Chávez AE, Chiu CQ & Castillo PE (2010). TRPV1 activation by endogenous anandamide triggers postsynaptic long-term depression in dentate gyrus. *Nat Neurosci* **13**, 1511–1518.

Gibson HE, Edwards JG, Page RS, Van Hook MJ & Kauer JA (2008). TRPV1 channels mediate long-term depression at synapses on hippocampal interneurons. *Neuron* **57**, 746–759.

Additional information

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Competing interests

None declared.