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Hagiwara S & Byerly L. Calcium channel. *Annu. Rev. Neurosci.* 4:69-125, 1981.
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This paper reviewed the properties of the membrane calcium (Ca) currents that had been studied, by 1979, in animals from *Paramecium to* mammals. Major emphasis was placed on the diversity of Ca currents and on the biophysical properties that distinguished Ca currents from the better studied Na and K currents. [The *SCI®* indicates that this paper has been cited in more than 1,070 publications, making it the most-cited publication in this journal.]

Dr. Hagiwara and Calcium Channels

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Susumu Hagiwara, or "Hagi" as he was called by all who knew him, died of heart failure on April 1, 1989. His hearth had been poor from the time he had tuberculosis as a medical student in Japan. He used to Joke with us that he had gotten to know the world from its hospitals, since he had been hospitalized on so many of his scientific travels.

I was just finishing my postdoctoral work at UCLA, and was about to start as an assistant professor at USC, when Hagi proposed I join him in writing this review, in large part, the review was based on discussions that arose at the daily "lunches" in Hagi's lab, which often lasted for several hours and included many visitors in addition to all members of the lab.

I never expected that this review would be so highly cited. Most of the citations are made to support the statement that calcium (Ca) channels are found in many different types of cells and play important rotes in many physiological functions. Many of the citations are also made to recognize with one reference the numerous pioneering studies Hagi made on Ca channels.

The introduction of the patch clamp technique[1] coincided with the appearance of our review and suddenly made the Ca currents of almost all tissues accessible to biophysical analysis. In our review, we identified the problems that had previously limited the rigorous study of Ca channels and listed the desirable features for any preparation used to study the biophysical properties of Ca channels. The patch clamptechnique provided many of these desirable features. Thus, inthe following years, there was an explosion in the number of studies that could address the questions raised in our review.

A major purpose of our review was to discuss biophysical properties that distinguished Ca channels from sodium (Na) channels and potassium (K) channels. We pointed out that the enormous gradient of Ca^{2*} across the membrane implied highly nonlinear open-channel I-V relations and prevented the measurement of reversal potentials for Ca currents. Bertil Wile's popular textbook[2] included these arguments and has contributed significantly to increasing the sophistication of the analysis of Ca currents. K.S. Lee and R.W. Tsien[3] almost immediately seemed to contradict our conclusion by measuring the reversal of current through the cardiac Ca channel. This important result demonstrated that the Ca channel had a finite permeability for K*. Our review focused on the binding of permeant and blocking divalent cations to the Ca channel, using a simple single binding site model. The discoveries that Ca channels carry monovalent currents at large positive potentials and when external divalent ions are removed led to permeation models with at least two binding sites for the Ca channel.[4,5]

Our review proved correct in concluding that there are many different types of voltage-dependent Ca channels. Even though no single-channel Ca currents had been recorded at that time, the evidence for distinct types of Ca channels was already compelling. The diversity of Ca channels has become one of the major themes of biophysical research in this last decade.[6] There have been many excellent reviews written on Ca channels since our review, but none have been so broad. Hagi studied Ca channels in numerous invertebrate species, as well as vertebrates and even plants. That breadth of interest, and Hagi's playful delight in the unexpected, probably gave our review its remarkable acceptance.

1. **Hamill O P, Marty A, Neher E, Sakmann B & Sigworth F J.** Improved patchclamp techniques for high-resolution current recording from cells and cell-free membrane patches. *Pfliigers Arch.* 391:85-100, 1981. (Cited 3,400 times.)
2. **Hille B.** *Ionic channels of excitable membranes.* Sunderland, MA: Sinauer Associates, 1984. (Cited 1,150 times.)
3. **Lee K S & Tsien R W**. Reversal of current through calcium channels in dialysed single heart cells. *Nature* 297:498-501, 1984. (Cited 295 times.)
4. **Hess P & Tsien R W**. Mechanisms of ion permeation through calcium channels. *Nature* 309:453-6, 1984. (Cited 295 times.)
5. **Almers W & McCleskey E W.** Nonselective conductance in Ca channels of frog muscles: calcium selectivity in a single-file pore. *J Physiol.—London* 353:585-608, 1984. (Cited 200 times.)
6. **Byerly L & Hagiwara S**. Calcium channel diversity. (Grinnell A D. Armstrong D L & Jackson M B, eds.) *Calcium and ion channel modulation.* New York: Plenum Press. 1988. p. 3-18.

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