This Week's Citation Classic®

Petersen O H & Maniyama Y. Calcium-activated potassium channels and their role in secretion. *Nature* 307:693-6, 1984. [MRC Secretory Control Research Group, Physiological Laboratory. University of Liverpool, England]

In many cell types a rise in the free cytosolic Ca^{2+} concentration causes release of cellular K^+ to the surroundings. The different plasma membrane ion channels through which this K^+ exit occurs were characterized by patch clamp single channel current recording and a novel hypothesis advanced for the role of Ca^{2+}-regulated K^+ release in secretory epithelial cells. [The *SCI*® indicates that this paper has been cited in more than 515 publications.]

Calcium-Activated Ion Channels and Secretion

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Early in 1983 I submitted an article to *Nature* describing quantification of Ca^{2+}-activated K^+ channels in exocrine cells by combined patch-clamp single-channel and whole-cell current recording as well as a novel hypothesis explaining the link between Ca^{2+}-activated K^+ release and isotonic fluid secretion. The article was rejected, but the letter from the editor suggested that a shorter version focusing entirely on the quantification of the K^+ channels could be published as a letter to *Nature*.[1] The editor also invited me to describe the new hypothesis in the context of a review article on Ca^{2+}-activated K^+ channels. I wrote the review, which became this *Citation Classic*®, together with Yoshio Maruyama (now associate professor of physiology at Jichi Medical School, Japan), who was at that time my closest collaborator.

The paper has been widely cited because it provided a convenient overview of the different classes of Ca^{2+} -activated K^+ channels and because it explained the role of such channels in epithelial cells. We had been surprised by the existence of voltage-sensitive Ca^{2+} -activated K^+ channels in the exocrine glands, since these epithelial cells were unable to fire action potentials. A role for such channels was therefore far from obvious. We found the clue in earlier results,[2] that had not been properly understood, In which cellular reuptake of K^+ after agonist-evoked K^+ release was acutely abolished by removal of either extracellular Cl^- or Na^+. Since then evidence for cotransport of Na^+, K^+ and Cl^- had been obtained in several ceil types including kidney tubules.[3] The novel features of our model for exocrine fluid secretion were that cycling of K^+ through channel and cotransport systems would allow net NaCI uptake through the basolateral membrane and that the rate of uptake would be directly linked to the rate of transport in the cycle of K^+ release and uptake. The point of regulation was the K^+ channel. An agonist-evoked increase in the cytosolic Ca^{2+} concentration would open the channel, evoking K^+ release and membrane hyperpolarization. The latter would provide negative feedback on channel opening, resulting in very fine regulation.

Our model received much support in the years following its publication. I had an opportunity to review it when the Physiological Society invited me to deliver their 1991 Annual Review Prize Lecture.[4]

At the time we wrote our article, the main challenge was to understand the mechanism by which agonist-evoked Ca^{2+} signals evoked ion and fluid transport. Since then, Ca^{2+} -sensitive ion currents have been used to monitor changes in the cytosolic Ca^{2+} concentration nearthe cell membrane,[s] and this has helped us to identify local subcellular cytosolic Ca^{2+} signals.[6]

1. **Maruyama Y, Petersen O H**, **Flanagan P & Pearson G T**. Quantification of Ca^{2+} -activated K^+ channels under hormonal control in pig pancreas acinar cells. *Nature* 305:228-32. 1983. (Cited 135 times.)
2. **Petersen O H.** Some factors influencing stimulation-induced release of potassium from the cat submandibular gland to fluid perfused through the gland. J. *Physiol—London* 208:431-47. 1970.
3. **Greger R & Schlatter E**. Presence of luminal K^+. a prerequisite for active NaCI transport in the cortical thick ascending limb of Henle's loop of rabbit kidney. *Pflügers Arch.—Eur. J. Physiol.* 392:92-4. 1981. (Cited 185 times.)
4. **Petersen O H.** Stimulus-secretion coupling: cytopiasmic calcium signals and [he control of ion channels in exocrine acinar cells. *J. Physiol—London* 448:1-51, 1992.
5. **Wakui M, Potter B V L & Petersen O H.** Pulsatile intraceliular calcium release does not depend on fluctuations in inositol trisphosphatc concentration. *Namrc* 339:317-20. 1989. (Cited 150 times.)
6. **Thorn P, Lawrie A M, Smith P, Gallacher D V & Petersen O H**. Local and global cytosolic Ca^{2+} oscillations in exocrine cells evoked by agonists and inositol trisphosphatc *Cell* 74(4):661-8, 27 August 1993.

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