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This Week's Citation Classic®

Foreman J C, Mongar J L & Gomperts B D. Calcium ionophores and movement of calcium ions following the physiological stimulus to a secretory process. *Nature* 245:249-51, 1973.
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The calcium ionophore A23187 transports calcium from the extracelluar compartment into cytosol in an isolated cell system, thereby raising the cytosolic calcium concentration. The paper proposes that the physiological stimulus that initiates the secretory response in the cell is the rise in the cytosolic calcium concentration and that it opens calcium channels in the membrane, allowing calcium to enter the cell. [The *SCI*® indicates that this paper has been cited in over 550 publications.]

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It all started when I was a graduate student attempting to define the role of calcium in the process of histamine release stimulated from mast cells by an antigen-antibody reaction. I was following up work by A. Goth and colleagues[1] that showed that only the phospholipid phosphatidylserine potentiated immunologically induced histamine release. Jack Mongar and I showed that this effect of phosphatidylserine increased the effectiveness of calcium in the mast cell, but we were at a loss about how to investigate the mechanism of action of the phospholipid. At this point we learned that Bastien Gomperts was interested in membrane phospholipids, and we sought his advice. It was the best thing that could have happened to us: it was a meeting of the minds that we all benefited from and without which we would have been the poorer.

Gomperts had never heard of mast cells until he met Mongar and me, and from then on he developed a deep interest in and a great enthusiasm for these cells, an interest that continues today. Gomperts brought to us an almost never-ending stream of ideas; one of his first contributions was to draw our attention to a paper by B.C. Pressman[2] that described the effect of a novel calcium ionophore, A23187. We immediately obtained some and soon discovered that it released histamine from mast cells in a calcium-dependent manner.

Looking back now, this was probably one of the most exciting times of my research career. It was clear that we had discovered a means of controlling the intracellular level of calcium in mast cells and had provided evidence that a rise in the intracellular concentration of calcium was a sufficient signal to the mast cell to release histamine. The implications of these findings were clear: here for the first time was a means of investigating the physiological effects of manipulating intracellular calcium ion concentration in a wide variety of cells and tissues.

Our experiments were written up and sent to *Nature*. The referees' reports were both favourable and enthusiastic, but the editorial staff of *Nature* was not quite so keen. It took quite a lot of pushing, as I recall, to convince them to publish the paper. In the end, of course, they relented and now, with the hindsight of the *Science Citation Index*®, I guess they are content that we fought for what we considered to be the right place to publish this manuscript.

Shortly after the paper appeared I received an understandably aggressive letter from Peter Reed pointing out that he had published the first description of A23187,[3] and that we had failed to cite this. It was a genuine oversight on our part. We had cited Pressman's paper simply because it was the first we had spotted, and we were relatively unfamiliar with the world of ionophores. An apology was sent to Reed and we cited him in later papers, but I am glad now to reveal in public the history of our error.

Following this work with A23187, it became clear that researchers needed to look at the changes in intracellular calcium levels that followed physiological stimuli to cells. The major advance in this area was the development of quin indicators by R.Y. Tsien and his associates.[4] Although cell availability makes it difficult to use quin in mast cells, it is gratifying to see evidence in the related rat basophilic leukaemia cells[5] that supports the hypothesis expressed in our paper. Alas, however, all is still not clear because patch-clamping techniques have thus far failed to detect these channels.[6]

Although we have yet to find a physiological function for the mast cell, there can be no doubt that it has taught us a considerable amount about cell biology.

1. **Goth A, Adams H R & Knoohuizen M.** Phosphatidylserine: selective enhancer of histamine release. *Science* 173:1034-5, 1971. (Cited 160 times.)
2. **Caswell A H & Pressman B C.** Kinetics of transport of divalent cations across sarcoplasmic reticulum vesicles induced by ionophores. *Biochem. Biophys. Res. Commun.* 49:292-8, 1972. (Cited 190 times.)
3. **Reed P W & Lardy H A.** A23187: a divalent cation ionophore. *J. Biol. Chem.* 247:6970-7, 1972. (Cited 930 times.)
4. **Tsien R Y.** A non-disruptive technique for loading calcium buffers and indicators into cells. *Nature* 290:527-8, 1981. (Cited 165 times.)
5. **Beaven M A, Rogers J, Moore J P, Hesketh T R, Smith G A & Metcalfe J C.** The mechanism of the calcium signal and correlation with histamine release in 2H3 cells. *J. Biol. Chem.* 259:7129-36, 1984. (Cited 50 times.)
6. **Lindau M & Fernandez J H.** IgE-mediated degranulation of mast cells does not require opening of ion channels. *Nature* 319:150-3, 1986.

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