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This Week's Citation Classic

Rubin R P. The role of calcium in the release of neurotransmitter substances and hormones. *Pharmacol. Rev.* **22**:389-428, 1970.
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This paper summarizes existing evidence regarding the actions of calcium and other cations on secretory systems. The nature of calcium's role in the secretory process is also considered, and parallelisms are drawn between stimulus-secretion coupling and excitation-contraction coupling in muscle. [The *SCI*® indicates that this paper has been cited in over 735 publications since 1970.]

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"In 1960, I began working as a graduate student in the laboratory of William Douglas in the department of pharmacology at the Albert Einstein College of Medicine in New York City. The project on which I embarked concerned the role of calcium and other cations in the mechanism of catecholamine release from the isolated perfused cat adrenal gland.

"We found that calcium, but not sodium or potassium, was the crucial cation required for eliciting catecholamine secretion with the physiological neurotransmitter acetylcholine or with excess potassium. Calcium was not only a necessary but also a sufficient factor for supporting secretion. The close correlation between the concentration of extracellular calcium and evoked secretion, taken together with the demonstrated increase in radiocalcium uptake into chromaffin cells with acetylcholine,[1] supported the concept that 'acetylcholine stimulation enhances the entry of calcium into the medullary chromaffin cells.'

"The role of calcium in synaptic transmission had been defined in the 1950s and 1960s by Sir Bernard Katz and his colleagues during their analysis of acetylcholine release from the frog neuromuscular junction. So, the work emanating from the laboratories of Katz[2] and Douglas[3] provided the impetus for others to investigate the role of calcium in secretory phenomena. Confirmation of calcium-regulated secretion was obtained first in adrenergic synapses and then in a number of other secretory systems. The 1970 paper in *Pharmacological Reviews* reviews these findings. I believe that the reason this review has been cited so frequently reflects the prodigious interest generated by the original work of Douglas and myself[4,5] and the extension of these findings consummated in Douglas's laboratory. Today, the pivotal role of calcium in *stimulus-secretion coupling* is even more entrenched in scientific thought than it was in 1970. A book that presents a timely account of advances in this ever-expanding field has recently been published.[6]

"But the nature of calcium's role is much more complex than that envisioned in 1970. Activation of secretory cells was then viewed from a narrow perspective, involving the influx of extracellular calcium caused by an increase in membrane permeability. Our present view must encompass multiple cellular pools of calcium participating in the secretory response of many cells —a concept that was only briefly alluded to in the 1970 review.

"We are still permitted to draw parallels between stimulus-secretion coupling and excitation-contraction coupling in muscle, and to consider the molecular mechanism of calcium's action as being somehow linked to exocytosis, as we did in 1970. Calcium is still viewed as the progenitor of intracellular signals, but cyclic nucleotides, prostaglandins, and other arachidonic acid metabolites must now be portrayed as putative messengers that mediate the actions of calcium in secretory cells. Paradoxically perhaps, we have even progressed to the point where one may acknowledge the possible existence of noncalcium-dependent mechanisms, possibly acting synergistically with calcium, to activate the secretory process.[7] But as in 1970, a clear picture of the fundamental action of calcium on the arcane machinery that controls the secretory apparatus still remains elusive."

1. **Douglas W W & Poisner A M.** On the mode of acetylcholine in evoking adrenal medullary secretion: increased uptake of calcium during the secretory response. *J. Physiol.—London* **162**:385-92, 1962. [Cited 130 times.]
2. **Katz B.** *The release of neural transmitter substances.* Springfield, IL: Charles C. Thomas, 1969. 60 p. [Cited 465 times.]
3. **Douglas W W.** Stimulus-secretion coupling: the concept and clues from chromaffin and other cells. *Brit. J. Pharmacol.* **34**:451-74, 1968. [Cited 830 times.]
4. **Douglas W W & Rubin R P.** The role of calcium in the secretory response of the adrenal medulla to acetylcholine. *J. Physiol.—London* **159**:40-57, 1961. [Cited 495 times.]
5. ..... The mechanism of catecholamine release from the adrenal medulla and the role of calcium in stimulus-secretion coupling. *J. Physiol.—London* **167**:288-310, 1963.
6. **Rubin R P.** *Calcium and cellular secretion.* New York: Plenum Press, 1982. 276 p.
7. **Kaibuchi K, Sano K, Hoshijima M, Takai Y & Nishizuka Y.** Phosphatidylinositol turnover in platelet activation; calcium mobilization and protein phosphorylation. *Cell Calcium* **3**:323-35, 1982.