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This Week's Citation Classic

Blaustein M P. The interrelationship between sodium and calcium fluxes across cell membranes. *Rev. Physiol. Biochem. Pharmacol.* 70:33-82, 1974.
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The sodium gradient across the plasma membrane influences the intracellular calcium concentration in a large variety of cells via a countertransport of Na for Ca ("Na/Ca exchange"). This article provided a comprehensive review of the subject. [The *SCI*® indicates that this paper has been cited in over 515 publications.]

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In 1966 my family and I moved to Cambridge, England. I expected to study squid axon electrophysiology with Alan Hodgkin and his colleagues. Fortuitously, however, Peter Baker proposed that we all study the sodium pump. In September Richard Steinhardt and I went to the marine laboratory at Plymouth (with Baker, who worked across the hall) to explore the activation of the squid axon Na pump by external cations. Within a month, Steinhardt and I uncovered a large ouabain-insensitive (and, thus, non-Na-pump-mediated) Na efflux in Na-free Li-containing media. This efflux was dependent upon external Ca, suggesting that it involved an exchange of Na for Ca.[1] Baker pointed out the parallels with R. Niedergerke's[2] observations on Na-dependent Ca movements in the frog heart.

With 15-hour workdays I had absolutely no time to read Niedergerke's article until the squid supply mercifully lapsed during a November gale. His article immediately convinced me that cardiac muscle also had a Na/Ca exchange system and that this was the missing link between Na pump inhibition and the cardiotonic action of digitalis.[1] I was so excited that I celebrated alone (the laboratory was deserted that stormy night) with a fine dinner at the Green Lantern Restaurant. I then returned to the library to reread Niedergerke's article before going to bed.

Later that month Hodgkin joined us in Plymouth, and we began the Na-dependent Ca^{45} influx and efflux experiments that he and I completed during the 1967 squid season.[1,3]

At the very same time, unbeknownst to us, Harald Reuter was studying Na/Ca exchange in mammalian cardiac muscle.[4] I met Reuter at the International Physiological Congress in Washington, when I returned to the US in 1968. We subsequently agreed to work together during the summer of 1971 in his laboratory in Bern, Switzerland, rather than in mine in St. Louis (for obvious reasons!). We studied Na/Ca exchange in vascular smooth muscle; our manuscript, in which we alluded to the possible role of Na/Ca exchange in hypertension, was rejected by *Nature* and *Science*.

Howard Rasmussen heard me lecture on Na/Ca exchange at the University of Pennsylvania and invited me to write an article for *Reviews of Physiology, Biochemistry and Pharmacology*. This review was written in the marvelous library of the Marine Biological Laboratory at Woods Hole, Massachusetts, during the summer of 1973, as I watched the sun rise each morning while my daughter, Laura, attended a bird-watching course and my son, Marc, slept at home (my wife, Ellen, was tied to a new job in St. Louis).

This review was the first (and is still the only) comprehensive review of Na/Ca exchange in a whole spectrum of tissues. Na/Ca exchange modulates the intracellular Ca concentration in most types of cells in higher animals. It thus plays a critical role in such Ca-regulated physiological processes as the control of cardiac contractility,[5] epithelial Na transport,[6] visual adaptation, and synaptic potentiation, and it may link Na metabolism to elevated blood pressure in salt-dependent hypertension.[7]

Baker, a key player in the Na/Ca exchange story, died prematurely on March 10, 1987. He was organizing a symposium to celebrate the 20th anniversary of our first preliminary reports on Na/Ca exchange in squid axons.

[Editor's note: Baker, Blaustein, Hodgkin, and Reuter are among the 250 most-cited primary authors in the 1984 *SCI*.[8]]

1. **Baker P F, Blaustein M P, Hodgkin A L & Steinhardt R A.** The influence of calcium on sodium efflux in squid axons. *J. Physiol.—London* 200:431-58, 1969. (Cited 625 times.)
2. **Niedergerke R.** Movements of Ca in frog heart ventricles at rest and during contractures. *J. Physiol.—London* 167:515-50, 1963. (Cited 225 times.)
3. **Blaustein M P & Hodgkin A L.** The effect of cyanide on the efflux of calcium from squid axons. *J. Physiol.—London* 200:497-527, 1969. (Cited 350 times.)
4. **Reuter H & Seitz N.** The dependence of calcium efflux from cardiac muscle on temperature and external ion composition. *J. Physiol.—London* 195:451-70, 1968. (Cited 110 times.)
5. **Sheu S-S & Blaustein M P.** Sodium/calcium exchange and regulation of cell calcium and contractility in cardiac muscle, with a note about vascular smooth muscle. (Fozzard H A, Haber E, Jennings R, Katz A & Morgan H, eds.) *The heart and cardiovascular system.* New York: Raven Press, 1986. p. 509-35.
6. **Taylor A & Windhager E E.** Cytosolic calcium and its role in the regulation of transepithelial ion and water transport. (Seldin D W & Giebish G, eds.) *The kidney: physiology and pathophysiology.* New York: Raven Press, 1985. p. 1297-322.
7. **Blaustein M P.** Sodium ions, calcium ions, blood pressure regulation and hypertension: a reassessment and a hypothesis. *Amer. J. Physiol.* 232:C165-73, 1977. (Cited 615 times.)
8. **Garfield E.** The 250 most-cited primary authors in the 1984 *SCI*. Parts 1&2. *Current Contents* (45):3-11, 10 November 1986; (46):3-13, 17 November 1986.

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