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Lüttgau H C & Niedergerke R. The antagonism between Ca and Na ions on the frog's heart. *J. Physiol.—London* 143:486-505, 1958. [Department of Biophysics, University College London, England]

The results presented suggest that the antagonistic action of calcium and sodium ions on the heartbeat is mediated by a ligand for the two ions in the cell membrane. Movement of this ligand during the action potential is able to induce contraction. [The *SCI*® indicates that this paper has been cited in more than 515 publications.]

Ca/Na Antagonism in the Frog's Heart

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During the academic year 1956-1957, I joined Rolf Niedergerke at University College London in experiments designed to examine the way in which the Ca-Na antagonism influences the strength of the heartbeat. First we tested W. Wilbrandt and H. Koller's finding[1] (which we were able to confirm) that the heartbeat depends on the ratio $[CA]/[Na]^2$ of the two ions in the external medium. To our surprise, the specificity of the mechanism involved was high; e.g., the effects of neither lithium nor potassium were similar to those of sodium. More detailed analysis showed that enhancement of the $[Ca]/[Na]^2$ ratio lowers the depolarization of the cell membrane that causes a given increase in contractile tension.

To interpret these results, we suggested that calcium and sodium ions attach to sites of a membrane compound that, even in combination with either calcium or sodium, bears an electric charge. When carrying calcium, this compound, taken to move within the membrane during the action potential, may lead to contraction. (After termination of our work, a mathematical model of this idea was proposed by A.L. Hodgkin and published in a subsequent review.[2]) That this mechanism is indeed able to generate transmembrane ion fluxes was shown in experiments with ^{45}Ca tracer in which a net uptake of calcium occurred when cells were exposed to media of increased $[Ca]/[Na]^2$ ratio.[3]

The influence of our work on subsequent research, our own and that of others, was twofold: (1) Complementing previous results obtained with calcium injected into single muscle fibers,[4] it stimulated experiments on the problem of excitation-contraction coupling. Indeed, much of my own work after that time[5] was concerned with this topic. (2) In 1968 and 1969, our idea of a common mechanism for cellular inward movement of calcium and sodium ions was extended by two groups[6,7] who showed that sodium inward movement is coupled to the outward movement of calcium (and calcium inward movement to the outward movement of sodium). This was followed by a significant series of studies, not yet concluded, in which different methods and types of cells have been used to clarify both the nature and operation of this calcium/sodium exchange.[8]

It should be mentioned that our work would not have been possible without the support of Bernard Katz, a refugee scientist from Nazi Germany who after the war encouraged the work of, among others, young German scientists. We are greatly indebted to him.

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2. **Lüttgau H C.** The role of calcium ions in excitation-contraction coupling. (Taccardi B & Marchetti G. eds.) *Electrophysiology of the heart.* Oxford, England: Pergamon Press, 1964. p. 87-95.
3. **Niedergerke R.** Calcium and the activation of contraction. *Experientia* 15:128-30, 1959.
4. **----------.** Local muscular shortening by intracellularly applied calcium. *J. Physiol.—London* 128:12-3, 1955.
5. **Lüttgau H C.** The action of calcium ions on potassium contractures of single muscle fibres. *J. Physiol.—London* 168:679-97, 1963. (Cited 245 times.)
6. **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 765 times.) [See also: **Reuter** H. Citation Classic. *Current Contents/Life Sciences* 31(45):13, 7 November 1988.}
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8. **Allen T J A, Noble D & Reuter H,** eds. *Sodium-calcium exchange.* Oxford, England: Oxford University Press, 1989. 332 p.

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