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Blaustein M P. Sodium ions, calcium ions, blood pressure regulation, and hypertension: a reassessment and a hypothesis. *Amer. J. Physiol.* 232:C165-73, 1977.
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This article was the first statement of the "Na pump inhibitor (natriuretic hormone)-Na/Ca exchange-hypertension hypothesis." The hypothesis explains how the tendency to retain sodium ultimately causes the elevation of blood pressure in humans (and animals) with salt-dependent hypertension. [The *SCI*® indicates that this paper has been cited in over 840 publications.]

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The seeds for this article were sown in 1971, when Harald Reuter invited me to spend the summer in Bern, Switzerland; we agreed to explore the possible role of Na/Ca exchange in the control of intracellular Ca^{2+} in vascular smooth muscle.[1] My ideas about its potential relevance to hypertension began to gel when I was invited to present an Introductory Lecture at one of the sessions of the 1976 Federation of American Societies for Experimental Biology meeting. I decided to speak about Na/Ca exchange in various types of muscle.

In reviewing the smooth muscle data and my data from crustacean muscle, I was struck by the evidence that the vascular muscle contracted in response to much smaller reductions in the Na^+ gradient than did barnacle muscle. This led me to realize that, in smooth muscle cells with maintained tone, the cytosolic free Ca^{2+} concentration must always be maintained above the contraction threshold (in contrast to skeletal muscles, which relax completely between twitches). I concluded that the Ca^{2+} gradient across the plasma membrane must be modulated and that Na/Ca exchange participates in this modulation.[2] This provided a direct link between Na^+ metabolism and vascular contractility (and blood pressure). I then tried to think of ways that excess dietary Na^+ and renal Na^+ retention might lead to an elevation of intracellular Na^+ (and thus, via Na/Ca exchange, to an increase in cell Ca^{2+}).

A review of the literature convinced me that the postulated natriuretic hormone ("third factor"), which appeared to behave like an "endogenous digitalis," fit as a missing link in the chain between retention of Na^+ and elevation of cell Ca^{2+}. Na^+ retention and plasma volume expansion should trigger the secretion of this hormone; the hormone's direct natriuretic action, as well as the pressure-induced natriuresis, should compensate for the tendency to volume expansion. I discussed my ideas with Paul DeWeer, who encouraged me to prepare an article on this subject for the new "Cell Physiology" section of the *American Journal of Physiology* (Paul was a member of the Editorial Board).

While my article was in press, F.J. Haddy and H.W. Overbeck's[3] review on volume-expanded hypertension appeared; they, too, invoked an "endogenous digitalis," but did not mention Na/Ca exchange. H.E. deWardener and G.A. MacGregor pointed out that Louis K. Dahl[4] had first suggested (in 1969) that a "sodium-excreting (natriuretic) hormone with hypertensinogenic capacity" appeared to play a role in the pathogenesis of salt-dependent hypertension.

The "natriuretic hormone-Na/Ca exchange-hypertension hypothesis" has been subjected to extensive testing during the past decade. There is evidence that many individuals with salt-dependent hypertension have a tendency to retain Na^+ and to expand blood volume.[5] The search for the elusive "endogenous digitalis," which appears to be present in relatively high concentrations in the plasmas of individuals with low-renin essential hypertension, may be reaching a climax with the recent report of its purification.[6] The physiological significance of Na/Ca exchange in the regulation of vascular smooth muscle cell Ca^{2+} has been controversial.[7] However, recent studies[8,9] clearly show that vascular smooth muscle, like most other types of muscle, contains a large-capacity Na/Ca exchanger that plays an important role in cell Ca^{2+} regulation, especially when cytosolic free Ca^{2+} exceeds the contraction threshold.

The seminal influence on my thinking was the aforementioned contrast between vascular smooth muscle and barnacle muscle Ca^{2+} metabolism. I am especially grateful to the American Heart Association for the grant-in-aid that supported my early work on barnacle muscle. Who would have thought that this seemingly esoteric research would lead to a new view of the pathogenesis of essential hypertension? It now gives me great pleasure to try to repay my debt to the Heart Association by serving as a member of its Research Committee.

1. **Blaustein M P.** Citation Classic. Commentary on *Rev. Physiol. Biochem. Pharmacol.* 70:33-82, 1974. *Current Contents/Life Sciences* 30(35):14, 31 August 1987.
2. ———. Sodium-calcium exchange and the regulation of cell calcium in muscle fibers. *Physiologist* 19:525-40, 1976. (Cited 35 times.)
3. **Haddy F J & Overbeck H W.** The role of humoral agents in volume expanded hypertension. *Life Sci.* 19:935-48, 1976. (Cited 225 times.)
4. **Dahl L K, Knudsen D K D & Iwai J.** Humoral transmission of hypertension: evidence from parabiosis. *Circ. Res.* 24-25(Supp.I):I-21-33, 1969. (Cited 120 times.)
5. **Hamlyn J M & Blaustein M P.** Sodium chloride, extracellular fluid volume, and blood pressure regulation. *Amer. J. Physiol.* 251:F563-75, 1986. (Cited 5 times.)
6. **Hamlyn J M, Harris D W & Ludens J H.** A digitalis-like compound from human plasma: purification and characterization. *FASEB J.* 2:A329, 1988.
7. **Brading A F & Lategan T W.** Na-Ca exchange in vascular smooth muscle. *J. Hypertension* 3:109-16, 1985. (Cited 20 times.)
8. **Blaustein M P, Ashida T, Goldman W, Wier W G & Hamlyn J M.** Sodium/calcium exchange in vascular smooth muscle: a link between sodium metabolism and hypertension. *Ann. NY Acad. Sci.* 488:199-216, 1986. (Cited 5 times.)
9. **Smith J B & Smith L.** Extracellular Na^+ dependence of changes in free Ca^{2+}, $^{45}Ca^{2+}$ efflux, and total cell Ca^{2+} produced by angiotensin-II in cultured arterial muscle cells. *J. Biol. Chem.* 262:17455-60, 1987.

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