Sodium pumps: ouabain, ion transport, and signaling in hypertension

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TO THE EDITOR: A recent Editorial Focus in this journal (7) addresses the newly recognized role of the sodium pump as both an ion transport protein and a hormone receptor with its own signaling cascade. The relative importance of the cardiotoxic steroids (CTS) as endogenous signaling hormones versus their ability to inhibit the sodium pump is of great interest. Indeed, the article noted that “although all digitallike compounds inhibit Na-K-ATPase-mediated transport, they differ considerably in terms of their hypertensive effects.” The author concludes that “these findings do not support the prevailing hypothesis that the pathophysiological effect of digitals results from inhibition of . . . transport activity.” This implies that the hypertensive effect of CTS may be due to the action of these agents as regulators of signal transduction, entirely unrelated “to its (Na-K-ATPase’s) role as an ion pump.” The discoveries related to Src kinase-mediated signal transduction by Na-K-ATPase add a new dimension to the view that the endogenous cardiotoxic steroids comprise a novel hormone system. Nevertheless, the view that CTS induced hypertension is unrelated to inhibition of ion transport is inconsistent with published reports. Regrettably, the Editorial Focus does not cite key articles that support the conclusion that CTS hypertension is secondary to inhibition of sodium pumps.

It is true that the tendency of certain CTS to induce hypertension does not correlate with their relative potency as Na-K-ATPase inhibitors (8, 9). The most obvious comparison is that ouabain induces hypertension while digoxin (1, 9) and a digitoxigenin derivative, PST-2238 (4), are antihypertensive. It is not need not imply that ouabain’s effect on blood pressure is unrelated to inhibition of Na+ transport. Instead, these data are consistent with the interpretation that some CTS have mixed agonist/antagonist properties.

Viability of the hypothesis that enhancement of cytoplasmic Ca2+ responses by ouabain is related to inhibition of Na-K-ATPase relies on the secondary effect of Na+/Ca exchange. There is now direct evidence that elevation of blood pressure is a consequence of reduced transport activity of the ouabain-sensitive Na-K-ATPase α2-isofrom (2, 3, 10) and the resultant Ca2+ gain mediated by Na/Ca exchange (3, 5, 10). Moreover, reduced α2 expression leads to murine hypertension (10). The vascular myogenic effect of that model is prevented by the Na/Ca exchange inhibitor SEA0400 (10). A key role for Na/Ca exchange is revealed by the observation that SEA0400 lowers blood pressure in ouabain-induced hypertension and other forms of salt-dependent hypertension, but not salt-independent hypertension (5). These findings demonstrate that ouabain’s hypertensive effect depends on its inhibition of the Na-K-ATPase and Ca2+ gain via Na/Ca exchange. Thus Src signaling, alone, appears to be insufficient to raise blood pressure in ouabain-induced hypertension although an accessory role is not excluded.

Comparison of the effect of reduced expression of the α2 Na-K-ATPase (6) with that of low-dose ouabain on cell signaling may be a useful way to determine the roles of altered Na+ and Ca2+ in mediating the effects of ouabain on Src kinase signaling.

REFERENCES


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