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cAMP-Dependent Protein Kinase (PKA) Stimulates Na/K ATPase in Guinea-Pig Ventricular Myocytes

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The Na/K pump, a plasma membrane ATPase, plays a key role in the regulation of intracellular Na ions and the maintenance of ionic gradients across cell membranes. Because the Na/K ATPase exchanges three intracellular Na ions for two external K ions, an outward pump current is generated. The Na/K pump current was estimated as that abolished by 0.5 mM strophanthidin in myocytes superfused with modified Na-containing Tyrode's at ~36℃ and internally dialyzed via pipettes perfused with solution including 50 mM Na^+, 10 mM MgATP, and 50 or 100 nM Ca^{2+}. Steady membrane current at potentials between -100 mV and +30 mV was measured near the end of 40-ms steps from the 0 mV holding potential. The steady-state Na/K pump current-voltage (I-V) relationship was obtained by subtracting the I-V relationship determined in the presence of strophanthidin from the average of those determined, just before and just after, in its absence. As previously reported, Na/K pump current showed a variable tendency to run down (in a voltage-independent manner) with time after breaking into the cell. We examined the influence on the Na/K pump I-V curve of maximally stimulating PKA with forskolin (2-10 μM), monitored via the consistent, concomitant increase in CFTR Cl^- channel current: the effects on the Na/K pump were more variable, and a similar range of effects was seen at 50 and 100 nM pipette [Ca^{2+}]. Thus, in 5 of the 28 myocytes examined the Na/K pump I-V relationship seemed unaltered by either forskolin or the passage of time, whereas in 6 other myocytes Na/K pump current appeared little affected by forskolin but similarly ran down in both its absence and presence. However, in 9 other myocytes Na/K pump current was reversibly increased (by ≤30%) by forskolin over the entire voltage range, and this stimulation was sometimes reproducible but often gradually declined with time after break-in. In 7 further myocytes, the strophanthidin-sensitive current in forskolin seemed contaminated by a strophanthidin-induced increase in Cl^- conductance (likely reflecting stimulation of CFTR or swelling-activated Cl^- channels), precluding analysis of forskolin action on the Na/K pump. So it appears that PKA, stimulated by forskolin, can increase Na/K pump current, but that caution must be exercised in equating cardiotonic steroid-sensitive current with that generated by the Na/K pump.