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On the importance and mechanism of amplification of digitalis signal through Na+/K+-ATPase.

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Therapeutic concentrations of digitalis drugs inhibit the proliferation of breast cancer cells by inducing the interaction of Na+/K+-ATPase with Src/EGFR, activation of ERK1/2, and the resulting upregulation of cell cycle inhibitor p21Cip1. Quantitative comparison of ouabain dose-response curves for growth arrest and pump inhibition shows that ratio of Ki (pump)/Ki (proliferation) = 7.2. Such large gains in sensitivity are characteristic of several signal transducing pathways of other receptors. Making the reasonable assumption that Na+/K+-ATPase is the only receptor for ouabain, the large amplification factor clearly shows that occupation of a small fraction of pumping Na+/K+-ATPase by digitalis drugs, or endogenous digitalis-like factors, is sufficient to cause near complete inhibition of cell growth. The likely causes of large amplification factor in the signaling function of Na+/K+-ATPase include (a) interactions among the protomers of Na+/K+-ATPase in the membrane; and (b) induced clustering of Na+/K+-ATPase oligomers with neighboring proteins. The upstream location of both mechanisms suggests that similar amplifications also occur in other cell types with different digitalis downstream effects; e.g., stimulation of proliferation or hypertrophy.

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