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Role of MAPK Signaling Pathway in Cardiac Steroids-Induced Increase in Heart Contractility in Zebrafish

Nahum Buzaglo, Haim Rosen, Hagit Cohen-Ben Ami, David Lichtstein
Department of Medical Neurobiology and Department of Microbiology and Molecular Genetics, Institute for Medical Research-Israel-Canada, The Hebrew University-Hadassah Medical School, Israel

Cardiac steroids (CS) such as digoxin, ouabain and bufalin increase the force of contraction of heart muscle and were widely used in Western and Eastern clinical practices for the treatment of heart failure and atrial fibrillation. Despite extensive research, the mechanism underlying CS actions have not been fully elucidated. The dogmatic explanation for CS-induced increase in heart contractility is that the inhibition of Na^+, K^+-ATPase by CS causes an increase in intracellular Na^+ which, in turn, attenuates the Na^+/Ca^{++} exchange, resulting in an increased intracellular Ca^{++} concentration, and hence greater contractility. However, recent observations led to the hypothesis that the ability of CS to modulate a number of intracellular signaling processes may be responsible for both short- and long-term changes in CS action on cardiac function. This hypothesis was tested in the preset study, using the zebrafish model and our ability to quantify heart function *in-vivo*. MAPK play an important role in the transmission of cell signaling through a transduction system to the cell nucleus, where they influence the expression of genes that regulate important processes: cell growth, proliferation and apoptosis. CS caused the activation of the MAPK pathway in zebrafish as reflected by an increase in ERK1/2 phosphorylation. CS also dose-dependently augmented *in-vivo* the force of contraction of heart muscle in zebrafish larvae, without altering heart rhythm. Importantly, specific inhibitors of Src (PP2) and ERK1/2 (U0126 and PD98059), at low concentrations that do not affect heart function, completely abolished the CS-induced increase in contractility. This is the first demonstration of the involvement of CS-induced signaling in the steroids' function *in-vivo*. Our results show that activation of the MAPK pathway by CS is a critical process and suggest that in addition to Na^+, K^+-ATPase inhibition, signal transduction via the MAPK pathway is obligatory for CS action.