Digoxin and ouabain induce P-glycoprotein by activating calmodulin kinase II and hypoxia-inducible factor-1alpha in human colon cancer cells.


Source

Department of Genetics, Biology and Biochemistry, University of Torino, Via Santena, 5/bis, 10126, Torino, Italy; Research Center on Experimental Medicine (CeRMS), Via Santena 5/bis, 10126 Torino, Italy. chiara.riganti@unito.it

Abstract

Digoxin and ouabain are cardioactive glycosides, which inhibit the Na+/K+-ATPase pump and in this way they increase the intracellular concentration of cytosolic calcium ([Ca2+](i)). They are also strong inducers of the P-glycoprotein (Pgp), a transmembrane transporter which extrudes several drugs, including anticancer agents like doxorubicin. An increased amount of Pgp limits the absorption of drugs through epithelial cells, thus inducing resistance to chemotherapy. The mechanism by which cardioactive glycosides increase Pgp is not known and in this work we investigated whether digoxin and ouabain elicited the expression of Pgp with a calcium-driven mechanism. In human colon cancer HT29 cells both glycosides increased the [Ca2+](i) and this event was dependent on the calcium influx via the Na+/Ca2+ exchanger. The increased [Ca2+](i) enhanced the activity of the calmodulin kinase II enzyme, which in turn activated the transcription factor hypoxia-inducible factor-1alpha. This one was responsible for the increased expression of Pgp, which actively extruded doxorubicin from the cells and significantly reduced the pro-apoptotic effect of the drug. All the effects of glycosides were prevented by inhibiting the Na+/Ca2+ exchanger or the calmodulin kinase II. This work clarified the molecular mechanisms by which digoxin and ouabain induce Pgp and pointed out that the administration of cardioactive glycosides may widely affect the absorption of drugs in colon epithelia. Moreover, our results suggest that the efficacy of chemotherapeutic agent substrates of Pgp may be strongly reduced in patients taking digoxin.

PMID:19647009