


## Research articles

## The Cardiac Glycosides Digitoxin, Digoxin and Ouabain Induce a Potent Inhibition of Glycolysis in Lung Cancer Cells

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## Abstract

Cardiac glycosides are promising anticancer drugs. We have recently shown that the cardiac glycosides digitoxin, digoxin and ouabain induce selective killing of lung cancer cells, and that the cytotoxicity of digitoxin against these cells occurs at concentrations below those observed in the plasma of cardiac patients treated with this drug (Oncogene, 2013. doi: 10.1038/onc.2013.229). Here we report that digitoxin, digoxin and ouabain induce a potent inhibition of glycolysis (glucose consumption and lactate production) in A549 cells at nanomolar concentrations. This inhibition was comparable to that observed with millimolar concentrations of the glycolysis inhibitor dichloroacetate, which is currently undergoing clinical trials for the treatment of cancer. Because platinum compounds are commonly used in the treatment of lung cancer, we tested the cytotoxicity of several combinations of cisplatin with each cardiac glycoside; these combinations induced synergistic, antagonistic or additive effects mainly depending on the order at which the drugs were added to the cells.

## Introduction

Cardiac glycosides, also known as cardiotonic steroids, are a group of natural steroidal compounds that contain an unsaturated lactone ring in their structure and have the ability to inhibit the Na<sup>+</sup>/K<sup>+</sup>-ATPase pump. This lactone moiety defines the two classes of cardiac glycoside: cardenolides (with the lactone 2-furanone) and bufadienolides (with the lactone 2-pyrone). Numerous cardiac glycosides have been isolated from plants (e.g. digitoxin, digoxin and ouabain) and several have also been found in amphibians and mammals (e.g. digoxin, ouabain and bufalin). Some cardiac glycosides are used in cardiology for the treatment of cardiac congestion and some types of cardiac arrhythmias. The mechanism by which these drugs affect cardiac contractility is known to be mediated by a highly specific inhibition of Na<sup>+</sup>/K<sup>+</sup>-ATPase [1-3].

Several reports published over the last several decades suggest that cardiac glycosides have anticancer potential [4-10]. Evidence suggests that some cardiac glycosides induce selective anticancer effects [4, 11-13], which may occur at concentrations commonly found in the plasma of patients treated with these drugs [13, 14]. Other reports suggest, however, that cardiac glycosides-induced cytotoxicity is not selective for cancer cells [15]. Some cardiac glycosides have shown potent and selective anticancer effects in mice xenografted with human malignant cells [16-19]; however, these results may be an experimental artifact caused by the ability of cardiac glycosides to kill human cells versus rodent cells rather than by their ability to kill cancer cells versus normal cells [13, 20]. The cardiac drugs digitoxin and digoxin, the semi-synthetic cardiac glycoside UNBS1450, and two extracts from Nerium oleander have entered clinical trials for the treatment of cancer (see <http://clinicaltrials.gov/> and references [6, 7, 9, 21]).

Recently, we observed that the cardiac glycosides digitoxin, digoxin and ouabain induced selective killing of lung cancer cells, and that the cytotoxicity of digitoxin against these cells occurred at concentrations below those commonly observed in the plasma of cardiac patients treated with this drug [13]. We have also recently observed that an extract from the cardenolide-containing plant Nerium oleander induced a marked inhibition of glycolysis in lung cancer cells [22]. In this article, we report that the cardiac glycosides digitoxin, digoxin and ouabain induce a potent inhibition of glycolysis in lung cancer cells at nanomolar concentrations. We also report that specific combinations of these cardiac glycosides with cisplatin may increase the cytotoxicity of this commonly used anticancer drug in lung cancer cells.

## Material and Methods

## Chemicals and cell lines

Digitoxin (97%), digoxin (98.6%), ouabain (95%), cisplatin (99.9%), and dichloroacetate (98%), were purchased from Sigma. The human A549 lung cancer cell line and the human embryo lung fibroblastic MRC-5 cell line were purchased from the European Collection of Cell Cultures. The cell lines were maintained in DMEM supplemented with 2 mM glutamine, 50 µg/mL penicillin, 50 µg/mL streptomycin and 10% fetal bovine serum, and were cultured at 37 °C in a humidified atmosphere containing 5% CO<sub>2</sub>. Cell culture reagents were obtained from Life Technologies.

## Assay for cytotoxic activity

The MTT assay is a colorimetric technique that allows the quantitative determination of cell viability. It is based on the capability of viable cells to transform the MTT salt (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) into a formazan dye. Exponentially growing cells were seeded into 96-well plates and drugs were added 24 h later. Following the incubation period specified in figure and table legends, medium was removed and 125 µL MTT (1 mg/mL in medium) was added to each well for 4 hours. Then, 80 µL 20% SDS in 0.02 M HCl were added, plates were incubated for 10 hours at 37 °C, and optical densities were measured at 540 nm on a multiwell plate spectrophotometer reader. Cell viability was expressed as percentage in relation to controls. All data were averaged from at least three independent experiments and were expressed as means ± standard error of the means (SEM).

## Inhibition of glycolysis

Glycolysis inhibition was assessed by measuring concentrations of glucose (initial product of glycolysis) and lactate (final product of glycolysis) in control and treated cells. Briefly, 10<sup>6</sup> cells were exposed in 6-well plates to the tested compounds for 8 h, and glucose and lactate concentrations were determined in cell supernatants by using the Accutrend® Plus analyzer together with Accutrend glucose strips and BM-Lactate Strips (Roche Diagnostics). After calibrating the instrument with glucose and lactate calibration strips, test strips were used to determine glucose and lactate levels via colorimetric-oxidase mediator reactions according to the manufacturer's instructions [23]. Results are expressed as percentage of lactate production and percentage of glucose consumption in relation to untreated cells, and are shown as means ± standard error of the means (SEM) of three independent experiments.

## Combination Index

A549 cancer cells were exposed for 44-48 h to several concentrations of each cardiac glycoside, cisplatin and each cardiac glycoside in combination with cisplatin (the cardiac glycosides were added 4 h before cisplatin or vice versa). Cell viability was assessed by the MTT assay. The parameter Combination Index (CI) was calculated with the computer software Compusyn. A CI value <0.90 is considered to be synergism and is represented by "++++" for very strong synergism (CI<0.10), "+++" for strong synergism (CI=0.10-0.30), "++" for synergism (CI=0.30-0.70), "+" for moderate

synergism (CI=0.70-0.85) and "+" for slight synergism (CI=0.85-0.90). A CI value between 0.90 and 1.10 corresponds with additive effect and is indicated with "+". A CI value >1.10 is considered to be antagonism and is represented by "-" for slight antagonism (CI=1.10-1.20), "--" for moderated antagonism (CI=1.20-1.45), "----" for antagonism (CI=1.45-3.30), "-----" for strong antagonism (CI=3.30-10.00) and "-----" for very strong antagonism (CI>10.00) [24].

#### Statistical analysis

All data were averaged from at least three independent experiments and were expressed as means  $\pm$  standard error of the means (SEM). For statistical analysis we used the t-test (paired, two-tailed). A P-value >0.05 is not considered statistically significant and is not represented by any symbol. A P-value <0.05 is considered to correspond with statistical significance and is indicated with an asterisk (\*), a P-value <0.01 is indicated with a double asterisk (\*\*), and a P-value <0.001 is indicated with a triple asterisk (\*\*\*).

## Results and Discussion

In a recent work we reported that the cardiac glycosides digitoxin, digoxin and ouabain were more cytotoxic on A549 lung cancer cells than on MRC5 non-malignant lung fibroblasts [13]. We showed that the IC<sub>50</sub> values (means  $\pm$  SEM, nM) for the cancer cell line and the normal cell line were, respectively, 7.39  $\pm$  0.6 and 77.5  $\pm$  12.4 for digitoxin, 8.0  $\pm$  1.3 and 65.1  $\pm$  13.2 for digoxin, and 5.3  $\pm$  0.4 and 29.4  $\pm$  4.5 for ouabain. These data are particularly relevant for digitoxin, as this drug was cytotoxic on the cancer cell line at concentrations below those commonly observed in the plasma of cardiac patients treated with this drug (20-33 nM). Here we provide graphs showing how the viability of both cell lines was affected by several concentrations of each cardiac glycoside and of the anticancer drug cisplatin (Illustration 1).

Cardiac glycosides are known inhibitors of the Na<sup>+</sup>/K<sup>+</sup>-ATPase pump. It has been known for some time that glycolysis is coupled to sodium and potassium transport processes, and that some cardiac glycosides (e.g., ouabain) can inhibit glycolysis in a variety of non-malignant cells [25, 26]. It has recently been found that cancer cells are more reliant on glycolysis for their survival than non-malignant cells (reviewed in [27, 28]). Based on these findings, we previously proposed that cardiac glycosides might inhibit glycolysis in cancer cells and that such inhibition might play a critical role in the selective cytotoxicity of some cardiac glycosides (e.g. digitoxin) towards cancer cells [5]. More recently, we showed that an extract from the leaves of the cardenolide-containing plant Nerium oleander induced a marked inhibition of glycolysis in lung cancer cells [22]. To test if digitoxin, digoxin and ouabain could inhibit glycolysis in A549 lung cancer cells, we exposed these cells to each cardiac glycoside for 8 h, and glucose and lactate concentrations were determined in cell supernatants. Results, represented in Illustration 2, show that A549 cells exposed to nanomolar concentrations of all three cardiac glycosides exhibited a marked reduction in glucose consumption (A) and lactate production (B), comparable to those observed in cells exposed to an equi-toxic concentration of the glycolysis inhibitor dichloroacetate (DCA, 10 mM). No significant changes in glucose consumption and lactate production were observed in cells exposed to cisplatin 32  $\mu$ M. Illustration 2C includes representative photographs of cells exposed for 8 h to each drug, where cell number and morphology can be appreciated. These photographs seek to show that the reduction in glucose consumption and lactate production induced by the cardiac glycosides is not caused by a reduction in cell number (fewer cells would consume less glucose and would produce less lactate). Knowing that glucose and lactate are, respectively, the initial and final products of glycolysis, our data indicate that digitoxin, digoxin and ouabain induce a marked inhibition of glycolysis in A549 lung cancer cells at nanomolar concentrations.

The inhibition of glycolysis induced by digitoxin, digoxin and ouabain (Illustration 2) may be mediated by their known ability to inhibit the Na<sup>+</sup>/K<sup>+</sup>-ATPase pump. Indeed, several mechanisms have been proposed to explain how the inhibition of the Na<sup>+</sup>/K<sup>+</sup>-ATPase pump can lead to glycolysis inhibition [5]. It has been proposed that the inhibition of the Na<sup>+</sup>/K<sup>+</sup>-ATPase pump would decrease glycolysis activity via inhibition of the key glycolytic enzyme phosphofructokinase (discussed in reference [5]). In addition, inhibition of the Na<sup>+</sup>/K<sup>+</sup>-ATPase pump may restrict the activity of sodium glucose transporters (SGLTs), which couple glucose entry into some types of cells with the activity of this pump [5]. These transporters are typically found in small intestine and renal epithelial cells; however, clinical data have revealed that these transporters (SGLT2) are overexpressed in lung cancer cells that have metastasized to other organs [29]. This suggests that SGLT2 plays a role in glucose uptake in the metastatic lesions of lung cancer, and that inhibition of the Na<sup>+</sup>/K<sup>+</sup>-ATPase pump by cardiac glycosides may inhibit glycolysis by reducing glucose entry into the cells. The inhibition of glycolysis induced by digitoxin, digoxin and ouabain in A549 lung cancer cells may therefore be caused by inhibition of the Na<sup>+</sup>/K<sup>+</sup>-ATPase pump, which would lead to both the inhibition of the glycolytic enzyme PFK and the inhibition of glucose entry into the cells.

The inhibition of glycolysis observed in lung cancer cells treated with digitoxin, digoxin and ouabain may play a role in their cytotoxicity. The main cellular roles of glycolysis are to provide building blocks for biosynthesis and ATP, and evidence suggests that inhibition of these processes may have a higher impact on the viability of cancer cells than on that of non-malignant cells. Indeed, glycolysis inhibition has been proposed to be an anticancer strategy to selectively kill cancer cells [27, 28]. Although here we report that digitoxin, digoxin and ouabain induce selective cytotoxicity against lung cancer cells and that they induce a potent inhibition of glycolysis in these cells, we cannot conclude that the inhibition of glycolysis is responsible for their selective anticancer activity. As discussed previously [22], evidence suggests that the expression and cellular location of Na<sup>+</sup>/K<sup>+</sup>-ATPase alpha subunits in different types of cells (i.e., rodent cells, human cancer cells and human non-malignant cells) may explain why different cells are more or less susceptible to the cytotoxic activity of cardiac glycosides [30-32]. The study of the possible association between the expression and cellular location of Na<sup>+</sup>/K<sup>+</sup>-ATPase alpha subunits and the ability of cardiac glycosides to inhibit glycolysis would help reveal whether the inhibition of glycolysis by these compounds plays a role in their selective cytotoxicity.

Most cancer chemotherapy regimens include a combination of drugs. Since platinum compounds are widely used in the treatment of lung cancer, we assessed the cytotoxic activity of digitoxin, digoxin and ouabain in combination with cisplatin in A549 lung cancer cells. Then, we calculated the parameter Combination Index (CI) with the computer software Compusyn; this parameter is based on the Chou-Talalay method and offers quantitative definition for additive effect, synergism, and antagonism in drug combinations [24]. A549 cells were exposed for 44-48 h to several concentrations of cisplatin, each cardiac glycoside and cisplatin in combination with each cardiac glycoside. Cell viability was then estimated with the MTT assay. Results are collected in Illustration 3 (digitoxin), Illustration 4 (digoxin) and Illustration 5 (ouabain), and show that these combinations induced synergistic, antagonistic or additive effects mainly depending on the concentrations of the drugs and on the order at which they were added to the cells. Evidence suggests that the Na<sup>+</sup>/K<sup>+</sup>-ATPase alpha1 subunit plays a role in the intracellular accumulation of cisplatin and that cardiac glycosides can reduce its intracellular accumulation [33]; this may help explain some antagonisms observed in these Illustrations. The synergisms observed in these Illustrations with some combinations might be caused by the ability of cardiac glycosides to circumvent a variety of resistance pathways discussed elsewhere [9, 10].

In summary, we report for the first time that the cardiac glycosides digitoxin, digoxin and ouabain induce a potent inhibition of glycolysis in lung cancer cells, which may participate in their selective cytotoxicity. We also show that specific combinations of these cardiac glycosides may increase the cytotoxicity of platinum compounds, which are commonly used in the treatment of lung cancer.

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## Competing Interests

The authors declare that they do not have conflicts of interest.

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