Screening for potential hazard effects from multitarget anthracyclines on vasculature

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Recent studies have shown that conjugation of doxorubicin (DOX) with NO-releasing groups gives rise to novel multitarget anthracyclines such as nitrooxy-DOX (NitDOX), capable to overcome drug resistance by decreasing the activity of ABC transporters via critical tyrosine residues nitration on the pumps (Chegaev et al., 2011). In addition, NitDOX preferentially accumulates in mitochondria and affects their function thus representing a prototype of a new class of multifunctional anthracyclines, which have cellular targets different from, and greater efficacy against drug-resistant tumor cells than the parent compound (Riganti et al., 2013).

The widely described anthracyclines toxicity, however, might limit their use. Therefore, the aim of this study was to investigate the vascular effects, as potential hazard, of two novel anthracycline derivatives, namely NitDOX and CC27904, by studying their mechanical actions in rat aorta rings (Fusi et al., 2000) and their cytotoxic activity in aortic A7r5 cells (Coronnello et al., 2005). DOX was used as reference compounds.

At high concentrations (≥ 1 μM) NitDOX partially antagonized phenylephrine-induced contraction in endothelium-denuded rings. Conversely, in endothelium-intact rings all drugs were ineffective. Drugs pretreatment did not affect the concentration-response curve to K^+. Notably, in A7r5 cells all compounds caused significant and time-dependent cytotoxicity in the concentrations range 1-10 μM.

Preliminary data shows that after 24-h incubation, NitDOX- and CC27904-induced decrease in A7r5 cells viability was mediated by apoptosis as suggested by the induction of a sub-G1 peak in the flow cytometry histogram of treated cells.

In conclusion, NitDOX and CC27904 promote relevant cytotoxic and apoptotic effects at concentrations comparable to those effective to exert antitumor activities and to accumulate in drug-resistant cells, although devoid of significant vascular properties.

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