Saponara *et al.: Intrinsic Activity*, 2016; **4**(Suppl.3):A1.4
http://www.intrinsicactivity.org/2016/4/S3/A1.4
published online: 5 September 2016

22nd Scientific Symposium of the Austrian Pharmacological Society: Joint Meeting with the Hungarian Society for Experimental and Clinical Pharmacology

Vienna, 8–10 September 2016

MEETING ABSTRACT

A1.4

Screening for potential hazardous effects of an H_2S-donating anthracycline on the cardiovascular system

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Background: Conjugation of doxorubicin (DOX) with H_2S donors gave rise to novel anthracyclines, such as CC2790A, which failed to inhibit topoisomerase II and displayed a more potent cytotoxic effect and higher intracellular retention than the parent compound in DOX-resistant U-2 OS osteosarcoma cells [1]. The well-known cardiovascular toxicity of anthracyclines, however, might limit their use.
Methods: Therefore, the aim of this study was to investigate CC2790A-induced effects on the mechanical activity of fresh and cultured rat aorta rings, on $Ca_V1.2$ channel current ($I_{Ca1.2}$) of aortic A7r5 cells as well as its cytotoxicity on A7r5, endothelial EA.hy926 cells, and H9c2 cardiomyocytes [1,2]. DOX was used as reference compound.
Results: At concentrations of ≥1 µM, DOX partially increased phenylephrine-induced contraction in fresh endothelium-intact rings, while CC2790A was ineffective. Conversely, in endothelium-denuded rings both drugs were ineffective. CC2790A and DOX did not affect the concentration–response curve to high KCl. In arteries cultured with both drugs for 7 days, CC2790A blocked both phenylephrine- and high-KCl-induced contractions at a concentration 10-fold higher than that of DOX. CC2790A, at the maximum concentration tested of 10 µM, exhibited a weak Ca^{2+}-antagonist property in single A7r5 cells. CC2790A and DOX exerted cytotoxic effects at concentrations > 1 µM or > 0.1 µM, respectively, in both EA.hy926 and A7r5 cells. DOX (0.01–1 µM), at variance with CC2790A (0.1–1 µM), induced cell-cycle arrest in G_0/G_1 phase and significantly increased the proportion of cells in the sub-G_0/G_1 phase. Furthermore, it caused apoptosis, as confirmed by phase-contrast microscopy (cell shrinkage, membrane blebbing, presence of apoptotic bodies and attachment loss), by phosphatidylserine externalization (annexin V/propidium iodide labelling) as well as DNA fragmentation (DAPI staining). CC2790A, retained within H9c2 cells like DOX, was significantly less toxic and produced lower amounts of intracellular reactive oxygen species than the lead.
Discussion: In conclusion, CC2790A is a novel H_2S-donating anthracycline characterized by a more favourable toxicological profile and a better efficacy towards drug-resistant cells. In the context of earlier attempts to use H_2S-donating drugs in cancer therapy, CC2790A is worthy of further investigations in preclinical and clinical settings.
Acknowledgements: This work was supported by the Italian Ministry for Instruction, Universities and Research (Futuro in Ricerca 2012, RBFR12SOQ1 to S.S.).

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