BRITISH PHARMACOLOGICAL SOCIETY

Sample Abstract

Title

Attenuation of doxorubicin cardiotoxicity and NADPH oxidase activation by the AT1 receptor antagonist, losartan

Introduction: The use of doxorubicin (DOX) chemotherapy is severely limited by a dose-dependent cardiotoxicity, which it thought to be due, at least in part, to increases in reactive oxygen species[1]. Several of the actions of Nox2 NADPH oxidase in cardiac remodelling are mediated *via* activation of angiotensin II, which is known to be increased by DOX. The aim of this study was to investigate whether DOX-induced cardiac dysfunction may be mediated via angiotensin II.

Method: Adult male C57BL/6J mice were injected (i.p.) with DOX (4 mg/kg at 0, 7 and 14 days) or saline alone ± losartan (Los, 10 mg/kg/day; pretreatment 7 days) and studied 4 weeks later using M-mode echocardiography and left ventricular (LV) catheterization for pressure-volume analysis[2]. In cardiomyocytes isolated using collagenase digestion, NADPH-dependent superoxide production was assessed using lucigenin (5µmol/L)-enhanced chemiluminescence[2] and mRNA expression by real-time RT-PCR. Data are given as mean±SEM (n animals) and analysis was performed using two factor ANOVA followed by unpaired Student's T-test, as applicable.

Results: In DOX-treated mice, administration of Los resulted in normalization of fractional shortening; tended to improve maximum rate of LV pressure rise ($LVdP/dt_{max}$) and reduce development of myocardial atrophy (Table 1). Similarly, acute Los treatment (10 µM) in isolated LV cardiomyocytes partially attenuated DOX (0.5 µM)-induced increases in NADPH oxidase activity (Fig.1) and mRNA expression of Nox2 (98±26 vs 28±9%, n=6) and Nox4 (112±28 vs 18±26%, n=6).

Table 1 Effect of Los on cardiac structure and function

	Control	Los	DOX	DOX+Los
Fractional shortening (%)	34.4 ±1.2 (10)	33.0 ±0.9 (5)	25.0‡ ±1.4 (10)	32.0* ±1.4 (7)
$LVdP/dt_{max}$ ($mmHgs^{-1}$)	9676 ±386 (10)	9345 ±401 (10)	7512‡ ±434 (10)	8182 ±339 (10)
ESPVR	2.43 ±0.42 (10)	2.51 ±0.39 (10)	1.64‡ ±0.12 (10)	2.46* ±0.32 (7)
LV Mass /Tibia length (mg/mm)	5.93 ±0.21 (9)	5.84 ±0.16 (7)	4.93‡ ±0.14 (10)	5.32 ±0.14 (11)

‡p<0.05 vs. Control, *p<0.05 vs. DOX

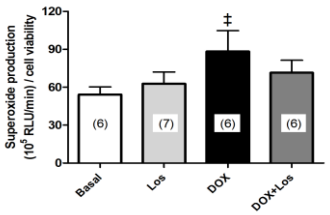

Fig. 1 Effect of Los on NADPH oxidase activity
‡P<0.05 vs Basal

Conclusion: Chronic treatment with Los prevented the development of myocardial dysfunction and the loss of cardiac mass associated with DOX treatment. Furthermore, increases in NADPH oxidase activity and mRNA expression of Nox isoforms induced by DOX *in vitro* were attenuated by co-treatment with Los. These data indicate that DOX-induced activation of Nox signalling in the context of cardiotoxicity may be mediated, at least to a certain extent, by angiotensin II.

References:

1. Octavia Y *et al*. (2012). *J Mol Cell Cardiol* **52**: 1213-1225.
2. Bendall JK *et al*. (2002). *Circulation* **105**: 293-296.

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