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Effect of doxorubicin, diltiazem or losartan on metabolism and catabolism of guanosine 5'-triphosphate in red blood cell in rats

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BACKGROUND AND OBJECTIVE

The importance of adenosine and ATP in regulating many biological functions has long been recognized, especially for their effects on the cardiovascular system (1) and may be used for monitoring therapeutic effects of anti-ischemia drugs (2). In response to ischemia, ATP is broken down to release adenosine. The activity of adenosine is very short lived because it is rapidly taken up by myocardial and endothelial cells, erythrocytes (RBC), and also rapidly metabolized to oxypurine metabolites and other adenine nucleotides (3). These metabolic events are known to occur in the myocardium as well as in erythrocytes (RBC) (2,4,5). We have shown earlier post exercise effect was associated with increased concentrations of ATP and GTP in RBC which may be used as biomarkers for cardiovascular protection (2), and that doxorubicin (DOX) increased breakdown of GTP more so than ATP in red blood cells (RBC)(6). In this study we compared the effect of DOX, diltiazem (DTZ) and losartan (LOS) on GTP metabolism in RBC using a freely moving rat model.

METHODS

Sprague Dawley (SD) rats (n = 5 – 11) were each given either 10 mg/kg of DOX or DTZ, 5mg/kg of LOS or normal saline by subcutaneous injection 2 times a day for 4 doses. Blood samples were collected just before the last injection (T0) and also at 0.08, 0.25, and 1hour after the last dose for measuring RBC concentrations of GTP and GDP. The average RBC concentrations of GTP, GDP and their ratios were compared and difference assessed by ANOVA followed by Tukey's and considered significant at $p < 0.05$ (Graphpad Prism 5, San Diego, CA, USA).

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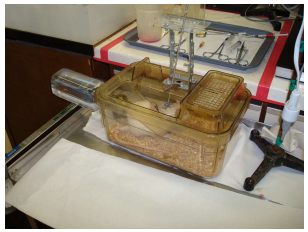
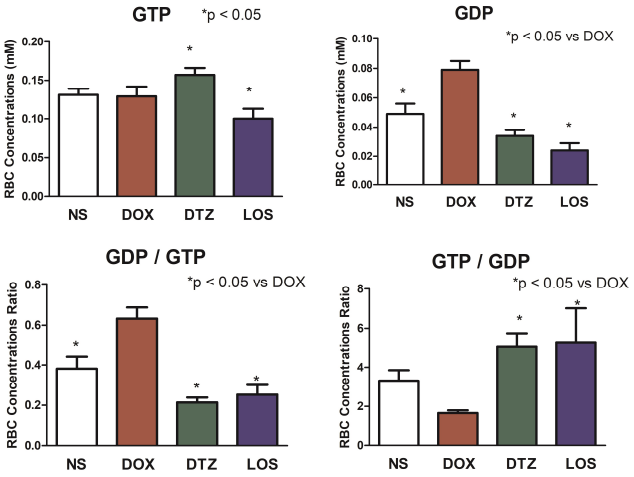
RESULTS AND DISCUSSION





- RBC concentrations of GDP and breakdown of GTP to GDP in the RBC were significantly higher in the DOX treated rats compared to the other groups ($p < 0.05$).
- Rats treated with DTZ or LOS had significantly greater production of GTP from GDP in the RBC compared to the DOX treated rats ($p < 0.05$).
- There was no difference in GTP metabolism between the DTZ and LOS treated rats ($p > 0.05$).

CONCLUSION

DOX (10 mg/kg) increased breakdown of GTP to GDP in the RBC. DTZ (10 mg/kg) or LOS (5 mg/kg) increased metabolism of GTP in the RBC suggesting that these cardiovascular agents may have potential to alleviate cardiotoxicity induced by DOX. Further studies are needed to substantiate the finding.

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