Inhibition of COX-1 attenuates lipopolysaccharide-induced decrease in GFR in mice

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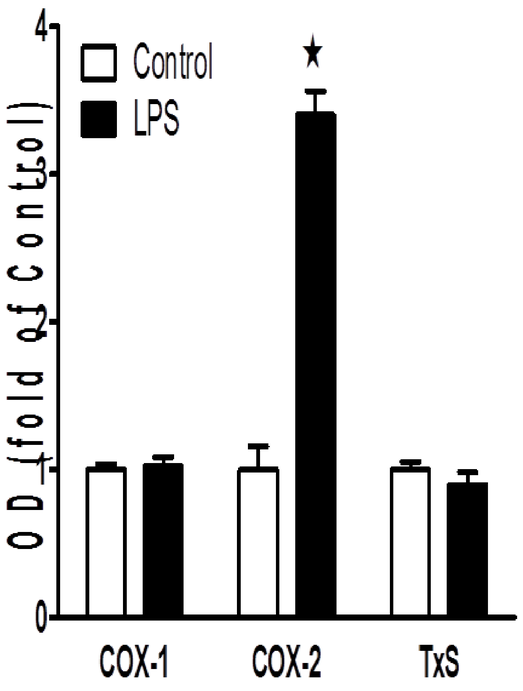
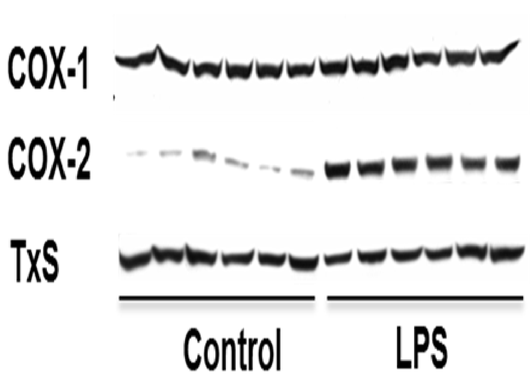
Introduction

Acute kidney injury (AKI) is a severe complication in septic patients and is clinically defined as a decrease in glomerular filtration rate (GFR). It has been suggested that the reduction in GFR results from vasoconstriction leading to an elevated resistance especially in afferent arterioles. The vasoconstrictive mediator thromboxane (Tx) A_2 might play an important role in the development of sepsis-induced AKI, because its receptors are localized in various parts of the kidney including the renal vasculature. The generation of TxA_2 from arachidonic acid depends on the activity of cyclooxygenases (COX 1 and 2). Therefore, the aim of this study was to assess the influence of COX-1- and COX-2-derived prostanoids on lipopoly-saccharide (LPS)-induced decrease in GFR in mice.

Results

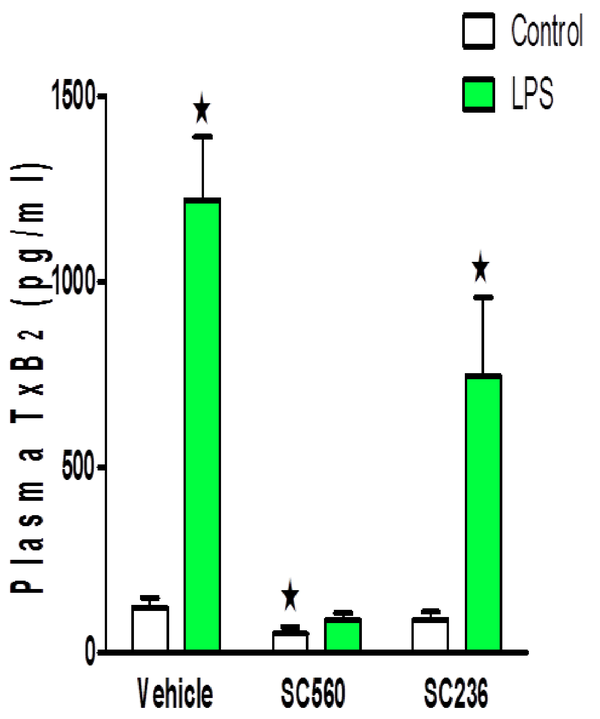
I. Renal expression of COX-1, COX-2 and TxS during endotoxemia:



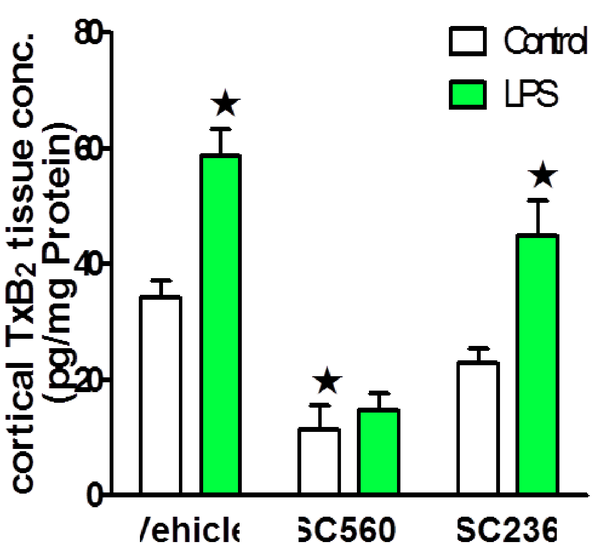


The protein abundance of renocortical COX-2 was increased in wild type mice four hours after LPS-injection (3mg/kg), whereas the levels of COX-1 and thromboxane synthase did not change during endotoxemia. ★P<0.05 vs LPS

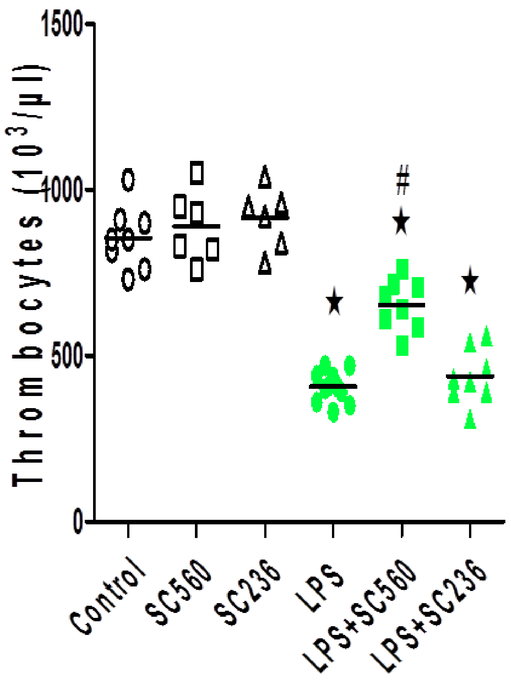
II. Effect of COX inhibition on TxB_2 concentration and platelet count:



The plasma thromboxane (Tx) B_2 concentration was elevated during endotoxemia. The increase of TxB_2 levels in response to LPS was abolished by inhibition of COX-1 (SC560, 20mg/kg), but was not changed by inhibition of COX-2 (SC236, 10mg/kg). ★P<0.05 vs vehicle-treated controls

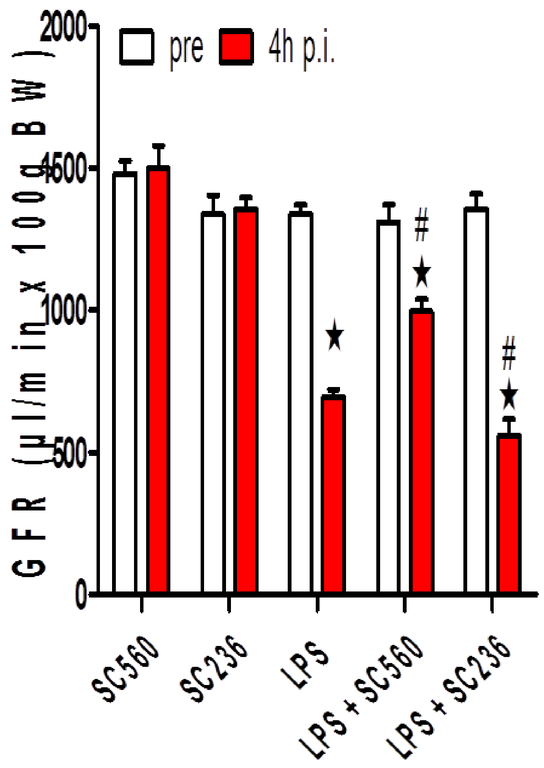


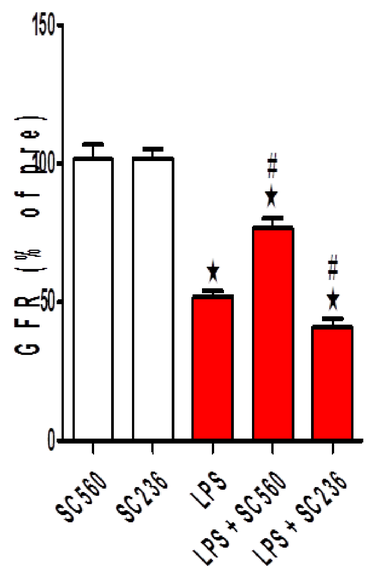
According to the changes in plasma TxB_2 levels, the renalcortical tissue concentration of TxB_2 was increased following LPS-injection. This effect was markedly reduced by inhibition of COX-1 (SC560), but not by inhibition of COX-2 (SC236). ★P<0.05 vs vehicle-treated controls



The amount of platelets was significantly reduced during endotoxemia. Pretreatment with the COX-1 inhibitor SC-560 attenuated the LPS-induced fall in thrombocytes to about 75% of basal levels. ★P<0.05 vs vehicle-treated controls; # P<0.05 vs LPS

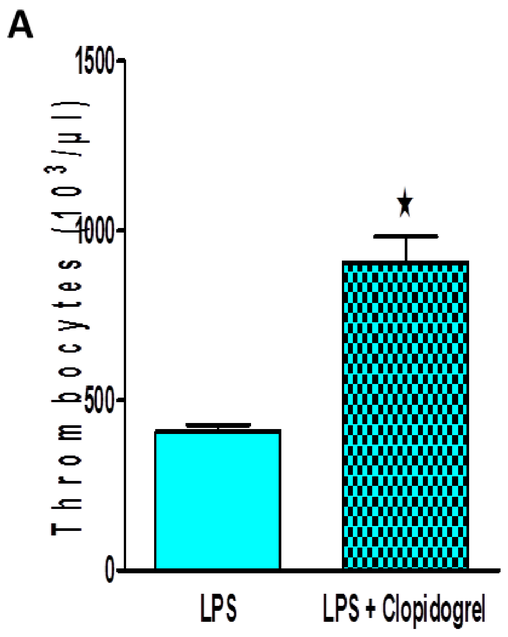
III. Effect of COX inhibition on GFR during endotoxemia:

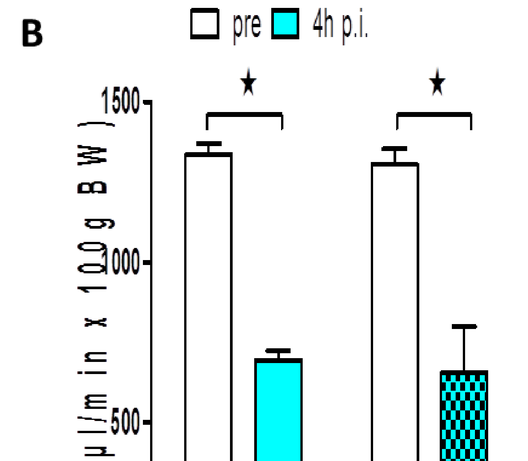




GFR was significantly reduced following LPS-injection. COX-1 inhibition (SC560) attenuated the endotoxemia-induced fall in GFR, whereas the COX-2 inhibitor SC236 enhanced the effect of LPS on GFR. Neither SC560 nor SC236 altered GFR under baseline conditions.
★P<0.05 vs vehicle-treated controls, #P<0.05 vs LPS

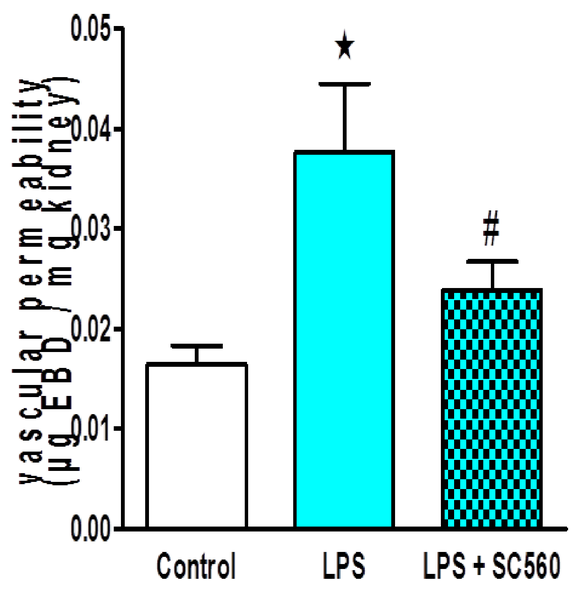
IV. Clopidogrel pretreatment-dependent effects on platelet count and GFR:





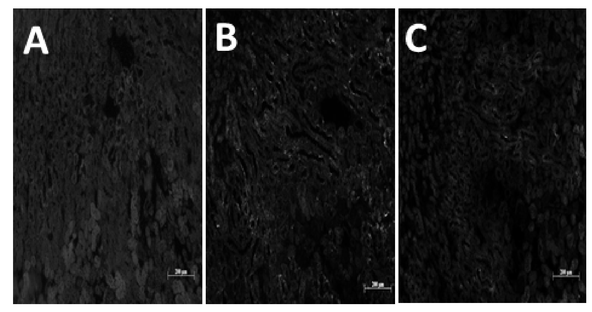
Pretreatment with the $P2Y_{12}$ receptor antagonist clopidogrel (10mg/kg) before LPS-injection abolished the LPS-induced fall in thrombozytes (A), but did not affect the decrease of GFR during endotoxemia (B). ★P<0.05 vs vehicle-treated controls,

V. LPS-induced changes in vascular permeability:



Renal vascular permeability as determined by Evans blue dye (20 mg/kg) increased following LPS-injection. Inhibition of COX1 reversed the endotoxemia-induced increase in evans blue dye extravasation. ★P<0.05 vs vehicle-treated controls, #P<0.05 vs LPS

VI. COX-1 inhibition reversed renal tubular hypoxia



Pimonidazole staining in kidney tissues was investigated to determine renal tissue hypoxia. (A) No staining was observed in vehicle-treated controls. (B) Pimonidazole staining revealed moderate hypoxic ares in cortical and outer medullary regions of lipopolysaccharide (LPS; 3 mg/kg; i.p.)-treated mice. (C) Pretreatment with the COX-1 inhibitor SC-560 (20 mg/kg; i.p.) for 30 min decreased the extent of hypoxia as indicated by pimonidazole staining.

Summary and Conclusion

- The endotoxemia-induced reduction in GFR is mediated in part by COX-1 derived prostanoids.
- Vascular- rather than thrombocyte-derived thromboxane seems to be responsible for the decrease in GFR during endotoxemia.
- Inhibition of COX-1 attenuates the LPS-induced increase in renal vascular permeability and renal tubular hypoxia
- Inhibition of COX1 might be a pharmacological target for treatment of sepsis-induced acute kidney injury.

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