

Poster presentation

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NPR-A gene deletion reverses vascular dysfunction associated with sepsis

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Background

Natriuretic peptides are a family of hormone/paracrine factors that play important roles in cardiovascular homeostasis. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), produced in the heart, bind to the particulate guanylate cyclase (pGC) linked natriuretic peptide receptor A (NPR-A) and generate the intracellular messenger cyclic guanosine 3',5'-monophosphate (cGMP). Via this receptor, ANP/BNP cause vasodilatation

and natriuresis, and are important in the regulation of blood pressure; mice lacking NPR-A exhibit hypertension and cardiac hypertrophy [1]. Since many cardiovascular disorders, including atherosclerosis and septic shock, are now accepted as inflammatory diseases of the vessel wall, elucidating potential roles for natriuretic peptides in regulating vascular inflammation could assist in the prevention and treatment of cardiovascular disease.

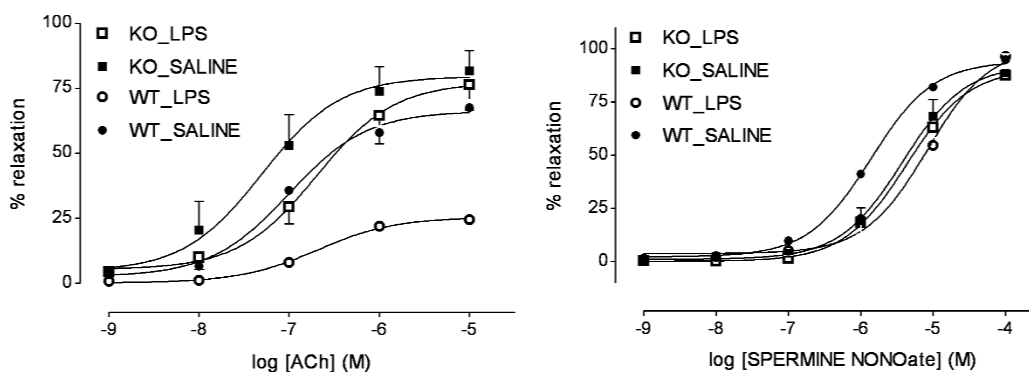


Figure 1

Concentration-response curves to ACh (*left*) and SPER-NO (*right*) in aortic rings from WT and NPR-A KO mice treated with LPS (12.5 mg/kg, i.v.) or saline for 16 h. Relaxation is expressed as mean \pm SEM percentage reversal of U46619-induced tone (n = 3–9).

Materials and methods

Male NPR-A knockout (KO) or wild type (WT; C57BL6) mice (25–30 g) were treated with 12.5 mg/kg i.v. *Salmonella typhimurium* lipopolysaccharide (LPS) or vehicle. After 16 h tissues (lung, aorta) were snap frozen and analysed for iNOS expression by western blot; plasma NO_x was measured by chemiluminescence. Endothelial and vascular (dys)function were assessed in isolated aortic rings using organ bath pharmacology. Vessels were pre-contracted with an ~EC₈₀ concentration of U46619 and concentration-response curves constructed to spermine NONOate (SPER-NO; 10⁻⁹–10⁻⁴ M), ANP (10⁻¹¹–10⁻⁶ M), and acetylcholine (ACh; 10⁻⁹–10⁻⁵ M).

Results

LPS administration *in vivo* caused a greater suppression of responses to U46619, ACh, ANP and SPER-NO in WT animals compared to NPR-A KO mice (Fig. 1). This differential effect on vascular function was paralleled by reduced iNOS expression (lung: 38.5 ± 6.3%* decrease, aorta: 80.3 ± 10.2%* decrease; *P < 0.05 vs saline control) and activity (plasma [NO_x]: WT saline 53.10 ± 5.156 μM, WT LPS 597.7 ± 34.98 μM, NPR-A KO saline 45.55 ± 6.054 μM, NPR-A KO LPS 387.2 ± 22.36 μM*; n = 7; *P < 0.05 vs WT).

Conclusion

Deletion of NPR-A *in vivo* results in reduced iNOS expression and vascular dysfunction associated with endotoxaemia. These data suggest that NPR-A activation (by ANP and/or BNP) can function as a pro-inflammatory mechanism that might assist in facilitating host defence in response to infection.

Acknowledgements

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References

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