sGC\(\alpha_1 \beta_1\) Attenuates Cardiac Dysfunction and Mortality in Murine Inflammatory Shock Models

BMC Pharmacology

Poster presentation

sGC$\alpha_1\beta_1$ attenuates cardiac dysfunction and mortality in murine inflammatory shock models

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from 4th International Conference of cGMP Generators, Effectors and Therapeutic Implications
Regensburg, Germany. 19–21 June 2009

Published: 11 August 2009

BMC Pharmacology 2009, **9**(Suppl 1):P5 doi:10.1186/1471-2210-9-S1-P5

This abstract is available from: http://www.biomedcentral.com/1471-2210/9/S1/P5

Background

Altered cGMP signaling has been implicated in myocardial depression, morbidity, and mortality associated with sepsis. Previous studies, using inhibitors of soluble guanylate cyclase (sGC), suggested that cGMP generated by sGC contributed to the cardiac dysfunction and mortality associated with sepsis. We used mice deficient in sGCα_1 (sGC$\alpha_1^{-/-}$mice) to unequivocally determine the role of sGC$\alpha_1\beta_1$ in the development of cardiac dysfunction and death associated with two models of inflammatory shock: endotoxin-induced and TNF-induced shock.

Results

At baseline, echocardiographic assessment and invasive hemodynamic measurements of left ventricular (LV) dimensions and function did not differ between WT and sGC$\alpha_1^{-/-}$mice on the C57BL/6 background (sGC$\alpha_1^{-/-B6}$ mice). Fourteen hours after a challenge with endotoxin, cardiac dysfunction was more pronounced in sGC$\alpha_1^{-/-B6}$ mice than in WT mice, as assessed using echocardiographic and hemodynamic indices of LV function. Similarly, Ca^{2+} handling and cell shortening were impaired to a greater extent in cardiac myocytes isolated from sGC$\alpha_1^{-/-B6}$ mice than in those from WT mice after a challenge with endotoxin. Importantly, morbidity and mortality associated with inflammatory shock induced either by endotoxin or TNF were increased in sGC$\alpha_1^{-/-B6}$ mice as compared to WT mice.

Conclusion

Together, these findings suggest that cGMP generated by sGC$\alpha_1\beta_1$ protects against cardiac dysfunction and mortality in murine models of inflammatory shock.