Enhanced sphingosine-1-phosphate levels by pharmacological or genetic approaches attenuate cardiac dysfunction in experimental septic cardiomyopathy

Enhanced sphingosine-1-phosphate levels by pharmacological or genetic approaches attenuate cardiac dysfunction in experimental septic cardiomyopathy

SM Coldewey, E Benetti, M Collino, M Bauer, A Huwiler, C Thiemermann.

Introduction: The role of Sphingosine-1-phosphate (S1P) and its receptors $S1PR_{1-5}$ in septic cardiomyopathy is not known. The S1P mimetic FTY720-P acts as an agonist on $S1PR_1$ and $S1PR_{3-5}$ and a functional antagonist on $S1PR_1$.

Methods: Cardiomyopathy was mimicked by co-administration of the bacterial cell-wall components lipopolysaccharide (LPS) and peptidoglycan (PepG) in wild-type (WT) and sphingosine kinase 2 deficient mice ($SPHK2^{-/-}$). At 1h after LPS/PepG mice received FTY720 alone, or they received a phosphatidylinositol 3 kinase (PI3K) inhibitor or a $S1P_2$ receptor antagonist prior to FTY720. 18h later cardiac function was assessed by echocardiography, serum-S1P was measured by LC/MS/MS and expression of signalling molecules was determined by immunoblot analysis.

Results: Compared to sham, mice subjected to LPS/PepG demonstrated a reduction in ejection fraction (EF) as well as a decrease of serum-S1P. In $SPHK2^{-/-}$-mice, which have higher endogenous S1P-levels, LPS/PepG-induced reduction of EF was lower than in WT-mice. Treatment with FTY720 attenuated the impaired EF in WT-mice accompanied by an increase of serum-S1P and an increased phosphorylation of AKT and eNOS in heart tissue. Cardioprotective effects of FTY720 were abolished following co-administration of either a PI3K inhibitor or a $S1PR_2$ antagonist. **Conclusion:** We show here for the first time that the impaired left ventricular systolic contractility caused by LPS/PepG is attenuated by a pharmacological or genetic approach to alter S1P-serum levels. Mechanistically, our results indicate that activation of $S1PR_2$ by increased serum S1P and the subsequent activation of PI3K signalling contribute to the observed cardioprotective effect of FTY720 in experimental sepsis.