Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol18Issue1abst059P.pdf

Effect of ikk inhibition on organ dysfunction associated with sepsis in mice with pre-existing diabetes

S. Al Zoubi[1], J. Chen[1], L. Martin[1], C. Murphy[1], F. Chiazza[2], D. Collotta[2], M. Collino[2], C. Thiemermann[1]. [1]Translational Medicine and Therapeutics, Queen Mary University of London, London, United Kingdom, [2]Department of Drug Science and Technology, University of Turin, Turin, Italy.

Introduction: Patients with type 2 diabetes mellitus (T2DM) have a higher incidence of infections and sepsis. Activation of nuclear factor-κB (NF-κB) plays a crucial role in the pathophysiology of sepsis and diabetes. Here we investigate i) whether pre-existing T2DM augments the organ dysfunction caused by sepsis and ii) whether inhibition of NF-κB using a selective IKK inhibitor attenuates the MOD in mice with pre-existing T2DM.

Methods: Ten-week old male C57BL/6 mice were randomized to high fat (HFD, 61% energy from fat) or chow diet for 12 weeks, and were then subjected to caecal ligation and puncture (CLP) or sham surgery (for 24 h) to cause moderate sepsis. At 1 h after CLP, mice received IKK-16 (1mg/kg in 2% DMSO, i.v.) or vehicle (2% DMSO, 3 ml/kg, i.v.).

Results: When compared to chow fed mice (n=18), mice on HFD (n=18) showed (i) a significant impairment in glucose tolerance [area under the curve (AUC): 29±0.5 vs. 47±3 g.min/dl, $P<0.05$], (ii) a small reduction in ejection fraction (72±1 vs. 64±1%, $P<0.05$) and, (iii) an increase in alanine aminotransferase (33±4 vs. 68±9U/L, $P<0.05$). Immunoblot analysis demonstrated significant increases in IKK and IκBα phosphorylation, translocation of p65 to the nucleus, and expression of inducible nitric oxide synthase (iNOS). When compared to mice on HFD subjected to sham (n=8), mice on HFD challenged with CLP (n=10) showed (i) a further decline in EF (63±1 vs. 32±4%, $P<0.05$), (ii) a further increase in serum ALT (100±16 vs. 368±68 U/L, $P<0.05$), and (iii) significant rises in urea (4±0.2 vs. 28±2 mmol/L, $P<0.05$) and creatinine (26±1 vs. 60±11 micromole/L, $P<0.05$). Administration of IKK-16 to mice on HFD (n=10) resulted in a significant reduction of the CLP-induced i) organ injury/dysfunction (EF: 53±3%, ALT: 186±33 U/L, urea: 17±3 mmol/L and creatinine: 30±7 micromole/L) and alterations in cardiac signalling when compared to HFD/CLP-mice treated with vehicle.

Conclusion: Our results show that HFD results in activation NF-κB (heart) and a small degree of cardiac dysfunction and liver injury. Moreover, a pre-existing diabetic phenotype worsened the organ injury/dysfunction and the degree of activation of NF-κB associated with CLP-sepsis. Most notably, inhibition of IKK reduced the activation of NF-κB and the organ injury/dysfunction caused by sepsis in animals with pre-existing T2DM. Thus, activation of NF-κB is a key, but not the only, driver of the cardiac dysfunction caused by sepsis in animals with T2DM.

References:

1. Casqueiro J *et al*. (2012). *Indian J Endocrinol Metab* **16**: 27-36.