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Potential pleiotropic effects of SGLT2- and DPP4- inhibitors, lessons learnt from rodent models

Introduction & Aim: Clinical trials have suggested that SGLT-2 inhibitors improved cardiovascular outcomes in patients with diabetes mellitus. We assessed whether the SGLT-2 inhibitor Dapagliflozin (Dapa) attenuates the upregulation of the cardiac Na^+/H^+ exchanger (NHE-1) *in vitro* in mouse cardio-fibroblasts stimulated with Lipopolysaccharides (LPS) and whether this effect is dependent on Adenosine Mono Phosphate Kinase (AMPK) activation.

Method: Mouse cardiofibroblasts were exposed for 16 hours to Dapa (0.4 μM), AMPK activator [A769662 (10 μM)], AMPK inhibitor [compound C (CC) (10 μM), an SGLT1 and SGLT2 inhibitor [Phlorizin (PZ) (100 μM)], Dapa+CC or Dapa+PZ and then stimulated with LPS (10 ng/ml) for 3 hours. NHE-1 mRNA levels were assessed by rt-PCR and total AMPK, phosphorylated-AMPK (P-AMPK), NHE-1 and Heat Shock Protein-70 (Hsp70) protein levels in the whole cell lysate by immunoblotting. In addition NHE-1 protein levels attached to Hsp70 were assessed by immuno precipitation.

Result: Exposure to LPS reduced P-AMPK levels. A769662 and Dapa equally increased P-AMPK. The effect was blocked by CC. Phlorizin had no effect on P-AMPK. LPS exposure significantly increased NHE-1 mRNA levels. Both Dapa and A769662 equally attenuated this increase. The effect of Dapa was blocked with CC. LPS significantly increased the concentration of NHE-1 attached to Hsp70. Both Dapa and A69662 attenuated this association and CC blocked the effect of Dapa. Again, Phlorizin had no effect and did not alter the effect of Dapa.

Conclusion: Dapa increases P-AMPK in cardiofibroblasts exposed to LPS. Dapa attenuated the increase in NHE-1 mRNA and the association between NHE-1 and Hsp70. This effect was dependent on AMPK.

Biography

Yochai Birnbaum is currently working as a Professor of Medicine and the John S. Dunn Chair in Cardiology Research and Education at the Section of Cardiology at Baylor College of Medicine. He has completed his graduation from Hadassah Medical School at the Hebrew University, Jerusalem, Israel. He has completed his Residency in Internal Medicine at Kaplan Medical Center, Rehovot, Israel and his Cardiology Fellowship at Rabin Medical Center, Petah-Tiqva, Israel. He has also completed a Research Fellowship in Cardiology at Good Samaritan Hospital and the University of Southern California, Los Angeles, California and Research Fellowship in Echocardiography at Cedars-Sinai Medical Center, Los Angeles, California.

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