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SGLT-2 inhibitors and the heart: Mechanisms of protection

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We assessed whether the SGLT-2 inhibitor dapagliflozin (Dapa) attenuates the upregulation of the cardiac Na^+/H^+ exchanger (NHE-1) *in-vitro* in mouse cardiofibroblasts stimulated with lipopolysaccharides (LPS) and whether this effect is dependent on adenosine monophosphate kinase (AMPK) activation. 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 three 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 immunoprecipitation. Exposure to LPS significantly reduced P-AMPK levels in the cardiofibroblasts. 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. Interestingly, none of the compounds significantly affected NHE-1 and Hsp70 protein levels in the whole cell lysate. However, LPS significantly increased the concentration of NHE-1 attached to Hsp70. Both Dapa and A769662 attenuated this association and CC blocked the effect of Dapa. Again, phlorizin had no effect and did not alter the effect of Dapa. 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 has completed his MD from the Hebrew University of Jerusalem, Israel. He is the John S Dunn Chair, Professor of Medicine at Baylor College of Medicine, Houston, Texas, USA. He has published more than 320 papers in reputed journals and has been serving as an Editorial Board Member of six journals.

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