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

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Purpose: 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 cardiofibroblasts stimulated with lipopolysaccharides (LPS) and whether this effect is dependent on adenosine monophosphate kinase (AMPK) activation.

Methods: Mouse cardiofibroblasts were exposed for 16h to Dapa (0.4μM), AMPK activator [A769662 (10μM)], AMPK inhibitor [compound C (CC) (10μM), an SGLT1 and SGLT2 inhibitor [phlorizin (PZ) (100μM)], Dapa+CC, or Dapa+PZ, and then stimulated with LPS (10ng/ml) for 3h. 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.

Results: 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.

Conclusions: 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 Professor of Medicine and the John S. Dunn Chair in Cardiology Research and Education at the Section of Cardiology. Baylor College of Medicine. He graduated Hadassah Medical School at the Hebrew University, Jerusalem, Israel. He completed his residency in Internal Medicine at Kaplan Medical Center, Rehovot, Israel and his cardiology fellowship at Rabin Medical Center, Petah-Tiqva, Israel. He 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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