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April 29-May 01, 2019 Kyoto, Japan

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47 Churchfield Road, London, W3 6AY, UK
: +44-203-7690-972
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4th World

Heart Congress

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Keynote Forum

Day 1

Yochai Birnbaum, J Clin Exp Cardiolog 2019, Volume 10
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4TH WORLD HEART CONGRESS

April 29-May 01, 2019 Kyoto, Japan

Yochai Birnbaum

Baylor Collge of Medicine, USA

SGLT-2 inhibitors and the heart: Mechanisms of protection

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 Mono Phosphate 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 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 immuno blotting. 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 A69662 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 Master's from the Hebrew University, Jerusalem, Israel. He is a Professor of Medicine at Baylor College of Medicine, Houston, Texas. He has published more than 320 papers in reputed journals and has been serving as an Editorial Board Member for many journals.

ybirnbau@bcm.edu

Notes:

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Yochai Birnbaum
Baylor College of Medicine, USA

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.

ybirnbau@bcm.edu

Notes:

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Zheng Sun
Baylor College of Medicine, USA

Epigenome regulation of myocardial metabolism in heart failure

Heart failure is a common cause of death in patients with obesity or diabetes. However, heart failure patients with higher BMI have better prognosis than patients with lower BMI. The relationship between myocardial glucose or lipid metabolism and cardiac contractile function is not clearly understood. We find that an epigenomic modifier, histone deacetylase 3 (HDAC3), is essential to protect the heart from obesity-induced heart failure. Mice with HDAC3 postnatally depleted in cardiac muscles (MCH3-KO) have normal cardiac functions on the normal chow diet, but display complete lethality due to severe hypertrophic cardiomyopathy and heart failure within four months on high-fat diet. Hyperglycemia, but not hyperlipidemia, precipitated heart failure in MCH3-KO mice. HDAC3 ChIP-seq analysis showed that the top DNA sequence motifs in HDAC3 binding site near down-regulated genes was binding sites of Estrogen Receptor (ER) and FOX family transcription factors known as pioneer cofactors for ER. Transcriptomics, metabolomics and isotope metabolic tracing revealed profound metabolic remodeling of glucose and lipid metabolism in cardiomyocytes depleted of HDAC3 or its related transcriptional factors. These findings shed light on the intricate epigenomic regulatory mechanisms connecting myocardial intermediary metabolism and cardiac contractile functions.

Biography

Zheng Sun has completed his PhD at University of Arizona and Postdoctoral training at University of Pennsylvania. He is the Assistant Professor at Baylor College of Medicine. He has published many seminal work and won several prestigious awards.

zheng.sun@bcm.edu

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