endothelial ERK2/thromboxane receptor pathway induces endothelial dysfunction, insulin resistance and steatohepatosis through superoxide with high fat high sucrose diet

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Introduction:

Metabolic syndrome (MetS) is well known as the risk of cardiovascular diseases associated with endothelial dysfunction and induces steatohepatosis. Insulin resistance is a major character of MetS, which affects intracellular signaling pathways and endothelial function. Extracellular signal-regulated kinase (ERK) is a major component of insulin signal and many of vasoactive peptides, which were released in MetS, can activate it in endothelium. However, the role of endothelial ERK in nitric oxide (NO) bioactivity in MetS in vivo has been unknown.

Purpose:

The aim of this study is to clarify the role of endothelial ERK2 on NO bioactivity in mice model of MetS.

Methods and Results:

We created endothelial specific ERK2 knock out mice (EE2KO) crossing Tie2-Cre mice and ERK2 flox mice and fed them with normal or high-fat/high-sucrose diet (HFHSD) for 24 weeks. Serum glucose and insulin levels and HOMA-IR were lowered in EE2KO with HFHSD without changing body weight. In wild type mice (WT) with HFHSD, nonalcoholic fatty liver disease (NAFLD) activity score, fibrosis score and serum ALT level were increased, all of which were blunted in EE2KO. EE2KO with HFHSD lowered systolic blood pressure (WT: 123.7±5.83 mmHg, EE2KO: 101.4±3.66 mmHg, P<0.01, N=8) without changing heart rate, which was increased to the same levels with L-NAME, an endothelial NO synthase inhibitor, in both groups. Serum NO levels measured with serum nitrite/nitrate concentrations were increased in EE2KO with HFHSD (WT: 23.10±3.74 µmol/l, EE2KO: 41.71±6.73 µmol/l, P<0.05, N=12). Endothelial function was assessed with the isometric tension measurement of aortic rings with acetylcholine (ACh). ACh-induced relaxation was improved in EE2KO with HFHSD. Superoxide production of aorta from EE2KO was lowered than WT with HFHSD in dihydroethidium (DHE) staining. S18886, an antagonist of the thromboxane A2-prostanoid (TP) receptor, decreased superoxide production of aorta in DHE staining resulting in improving endothelial function in the isometric tension measurement of aortic rings. Oral administrations of S18886 decreased systolic blood pressure, serum fasting glucose and insulin levels, and surprisingly improved steatohepatosis by decreasing NAFLD activity score and fibrosis score.

Conclusions: Endothelial ERK2/TP receptor pathway increases superoxide production and decreased NO bioactivity, resulting in deteriorating endothelial function, insulin resistance and steatohepatosis, which were improved by antagonist of the TP receptor in mice model of MetS. The present study indicates that ERK2/TP pathway could be a therapeutic target for complications of MetS.
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