論 文 要 旨

Luseogliflozin and caloric intake restriction increase superoxide dismutase 2 expression, promote antioxidative effects, and attenuate aortic endothelial dysfunction in diet-induced obese mice

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Aims/Introduction: The mechanisms underlying the effect of sodium-glucose cotransporter 2 (SGLT2) inhibitors on aortic endothelial dysfunction in diet-induced obesity are not clearly understood. In this study, we investigated whether SGLT2 inhibition by luseogliflozin improved free fatty acid (FFA)-induced endothelial dysfunction in high-fat diet (HFD)-induced obese mice.

Materials and Methods: Mice were fed a control diet or HFD for 8 weeks, and then each diet with or without luseogliflozin was provided for an additional 8 weeks under free or paired feeding. Afterward, the thoracic aortas were removed and utilized for the experiments.

Results: Luseogliflozin treatment decreased body weight, fasting blood glucose, insulin and total cholesterol in HFD-fed mice only under paired feeding but not under free feeding. Endothelial-dependent vasodilation under FFA exposure conditions was significantly lower in HFD-fed mice than in control diet-fed mice, and luseogliflozin treatment ameliorated FFA-induced endothelial dysfunction. Reactive oxygen species (ROS) production induced by FFA was significantly increased in HFD-induced obese mice. Luseogliflozin treatment increased the expression of superoxide dismutase 2 (SOD2), an antioxidative molecule, and reduced FFA-induced ROS production in the thoracic aorta. SOD reversed FFA-induced endothelial dysfunction in HFD-fed

mice.

Conclusions: We showed that caloric restriction is important for the effect of luseogliflozin on metabolic parameters and endothelial dysfunction. Furthermore, SGLT2 inhibition by luseogliflozin possibly ameliorates FFA-induced endothelial dysfunction by increasing SOD2 expression and decreasing ROS production in the thoracic aorta.