Repeated Glucose Spikes and Insulin Resistance Synergistically Deteriorate Endothelial Function and Bardoxolone Methyl Ameliorates Endothelial Dysfunction

論 文 要 旨

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Background

Both insulin resistance and postprandial glucose spikes are known for their potential to induce vascular endothelial dysfunction in individuals with metabolic syndrome. However, these factors are inextricable, and therefore, their relative contributions to inducing endothelial dysfunction remain elusive. In this study, we aimed to disentangle the effects of these factors and clarify whether bardoxolone methyl (CDDO-Me), a novel nuclear factor erythroid 2-related factor 2 (Nrf2) activator, protects against glucose spike-induced endothelial dysfunction.

Methods

We induced glucose spikes twice daily for a duration of 1 week to rats fed a standard/control diet (CD) and Western-type diet (WTD). Endothelium-dependent relaxation (EDR) was evaluated using isolated thoracic aortas. Gene expression and dihydroethidium (DHE)-fluorescence studies were carried out; the effect of CDDO-Me on aortic endothelial dysfunction in vivo was also evaluated.

Results

Neither WTD-induced insulin resistance nor pure glucose spikes significantly deteriorated EDR. However, under high-glucose (20 mM) conditions, the EDR of thoracic aortas of WTD-fed rats subjected to glucose spikes was significantly impaired. In this group of rats, we observed significantly enhanced DHE fluorescence as a marker of reactive oxygen species, upregulation of an oxidative stress-related gene (NOX2), and downregulation of an antioxidant gene (SOD2) in the thoracic aortas. As expected, treatment of the thoracic aorta of this group of rats with antioxidant agents significantly improved EDR. We also noted that pretreatment of aortas from the same group with CDDO-Me attenuated endothelial dysfunction, accompanied by a correction of the redox imbalance, as observed in gene expression and DHE fluorescence studies.

Conclusions

For the first time, we showed that insulin resistance and glucose spikes exert a synergistic effect on aortic endothelial dysfunction. Furthermore, our study reveals that CDDO-Me ameliorates endothelial dysfunction caused by glucose spikes in a rat model of metabolic syndrome.