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A new class of glycomimetic drugs to prevent free fatty acid-induced endothelial dysfunction

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Background: Carbohydrates play a major role in cell signaling in many biological processes. We have developed a set of glycomimetic drugs that mimic the structure of carbohydrates and represent a novel source of therapeutics for endothelial dysfunction, a key initiating factor in cardiovascular complications.

Purpose: Our objective was to determine the protective effects of small molecule glycomimetics against free fatty acid-induced endothelial dysfunction, focusing on nitric oxide (NO) and oxidative stress pathways.

Methods: Four glycomimetics were synthesized by the stepwise transformation of 2,5-dihydroxybenzoic acid to a range of 2,5-substituted benzoic acid derivatives, incorporating the key sulfate groups to mimic the interactions of heparan sulfate. Endothelial function was assessed using acetylcholine-induced, endothelium-dependent relaxation in mouse thoracic aortic rings using wire myography. Human umbilical vein endothelial cell (HUVEC) behavior was evaluated in the presence or absence of the free fatty acid, palmitate, with or without glycomimetics (1μM). DAF-2 and H2DCF-DA assays were used to determine nitric oxide (NO) and reactive oxygen species (ROS) production, respectively. Lipid peroxidation colorimetric and antioxidant enzyme activity assays were also carried out. RT-PCR and western blotting were utilized to measure Akt, eNOS, Nrf-2, NQO-1 and HO-1 expression.

Results: Ex vivo endothelium-dependent relaxation was significantly improved by the glycomimetics under palmitate-induced oxidative stress. In vitro studies showed that the glycomimetics protected HUVECs against the palmitate-induced oxidative stress and enhanced NO production. We demonstrate that the protective effects of pre-incubation with glycomimetics occurred via upregulation of Akt/eNOS signaling, activation of the Nrf2/ARE pathway, and suppression of ROS-induced lipid peroxidation.

Conclusion: We have developed a novel set of small molecule glycomimetics that protect against free fatty acid-induced endothelial dysfunction and thus, represent a new category of therapeutic drugs to target endothelial damage, the first line of defense against cardiovascular disease.