Long-Term Exposure to High Glucose Impairs Proliferation and Function of Endothelial Progenitor Cells by Modifying Nitric Oxide-Related but Not Oxidative Stress-Mediated Mechanisms.

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摘要

Abstract

OBJECTIVE—Endothelial progenitor cells (EPCs) are impaired in diabetes. This study aimed to investigate the direct effects of high glucose on EPCs.

RESEARCH DESIGN AND METHODS—Mononuclear cells isolated from healthy subjects were incubated with glucose/mannitol or drugs for EPC study. After 4 days of culture, attached early EPCs appeared. The monolayer late EPCs with cobblestone shape appeared at 2–4 weeks. Various immunofluroscence stainings were used to characterize the early and late EPCs. Senescence assay and the activity of endothelial nitric oxide synthase (eNOS) were determined. Migration and tube formation assay were done to evaluate the capacity for vasculogenesis in late EPCs.

RESULTS—Chronic incubation with high glucose but not mannitol (osmotic control) dose-dependently reduced the number and proliferation of early and late EPCs, respectively. High glucose enhanced EPC senescence and impaired the migration and tube formation of late EPCs. High glucose also decreased eNOS, FoxO1, and Akt phosphorylation and bioavailable nitric oxide (NO) in both EPCs. The effects of high glucose could be ameliorated by coincubation with NO donor sodium nitroprusside or p38 mitogen–activated protein kinase inhibitor and deteriorated by eNOS inhibitor or PI3K (phosphatidylinositol 3 ´ -kinase) inhibitor. Antioxidants including vitamin C, N-acetylcysteine – and polyethylene glycol (PEG)-conjugated superoxide dismutase, and PEG-catalase had no effects, whereas pyrrolidine dithiocarbamate, diphenyleneiodonium, apocynin, and rotenone even deteriorated the downregulation of both EPCs.

CONCLUSIONS—High glucose impaired the proliferation and function of early and late EPCs. NO donor but not antioxidants reversed the impairments, suggesting the role of NO-related rather than oxidative stress–mediated mechanisms in hyperglycemia-caused EPC downregulation.