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Acute hyperglycemia abolishes cardioprotection by remote ischemic perconditioning

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Background: Remote ischemic perconditioning (RIPerC) has a promising therapeutic value to improve prognosis of acute myocardial infarction. Chronic comorbidities such as diabetes are known to interfere with conditioning interventions by modulating cardioprotective signaling pathways, such as e.g. autophagy. However, the effect of acute hyperglycemia on RIPerC has not been studied so far. Therefore, here we investigated the effect of acute hyperglycemia on the cardioprotective effect of RIPerC.

Methods: Wistar rats were divided into normoglycemic (NG) and acute hyperglycemic (AGH) groups. Acute hyperglycemia was induced by glucose infusion to maintain a serum glucose concentration of 20-22 mM throughout the experimental protocol. NG rats received mannitol infusion of an equal osmolarity. Both groups were subdivided into an ischemic (Isch) and a RIPerC group. Each group underwent reversible occlusion of the left anterior descending coronary artery (LAD) for 40 min in the presence or absence of acute hyperglycemia. After 10 min LAD occlusion, RIPerC was induced by 3 cycles of 5 min unilateral femoral artery and vein occlusion and 5 min reperfusion. After 120 min reperfusion, infarct size was measured by triphenyltetrazolium chloride staining. To study underlying signaling mechanisms, hearts were harvested for immunoblotting after 35 min in both the NG and AGH groups.

Results: Infarct size was significantly reduced by RIPerC in NG, but not in the AGH group (NG: Isch: 24.65 ± 7.45%, p < 0.05; AGH: Isch: 54.19 ± 4.07% vs. 52.76 ± 3.80%). Acute hyperglycemia per se did not influence infarct size, but significantly increased the incidence and duration of arrhythmias. Acute hyperglycemia induced autophagy, as LC3 III/LC3 I ratio decreased and phosphorylated 56k increased possibly via the phosphorylation of Akt. Furthermore, acute hyperglycemia significantly elevated the nitrative stress in the heart (0.08 ± 0.01 vs. 0.50 ± 0.04 μmol 3-nitrotyrosine/mg protein, p < 0.05).

Conclusions: This is the first demonstration that acute hyperglycemia deteriorates cardioprotection by RIPerC. The mechanism of this phenomenon may involve an increased nitrative stress and decreased myocardial autophagy induced by acute hyperglycemia.

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Deregulation of thioredoxin system contributes to monocyte dysfunction in diabetes mellitus: Implications for impaired arteriogenesis in type 2 diabetic patients

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Background: A close association connects Gamma-GlutamylTransferase (GGT) activity to acute thrombotic events that coexisting diabetes increases exponentially. Tissue Factor (TF), the leading factor of acute thrombotic complications, is also coexpressed with GGT in atherosclerotic plaques raising the issue of a direct contribution of GGT to TF activation, a possibility never explored in vivo. Aim: To assess the effect of an enzymatically inactive human recombinant (hr) GGT on TF antigen (ag), TF mRNA and TF pro-coagulant activity (PCA) in human peripheral blood mononuclear cells (PBMCs). Experiments were conducted in both normal (NG, 10 mM) and high (HG, 50 mM) glucose concentrations, the diabetic hallmark.

Methods: PBMCs obtained from healthy donors (discontinuous Ficoll/Hystopaque density gradient) were incubated with hrGGT (0.5 ng/mL) either alone or with anti-hrGGT, a specific polyclonal antibody (2.5 μg/mL). Because of the pivotal role played by NFkB, a redox-sensitive transcription factor encoding TF, we also evaluated the effect Nfκb inhibition by BAY-11-7082 (10-SM) and N-acetylcysteine (NAC) (10-3M), an antioxidant. TF PCA (1-stage clotting assay, arbitrary units), αL (ELISA, pg/mL) and mRNA (real-time PCR, normalized-fold expression compared to housekeeping genes) were the evaluation variables.

Results: hrGGT increased TF PCA (from 0.008 ± 0.007 to 0.37 ± 0.3, n=14, p<0.001), αL (from 85 ± 59 to 36 ± 32, n=13, p<0.001) and mRNA (from 0.006 ± 0.002 to 0.048 ± 0.04, n=9, p<0.001) an effect inhibited by anti-hrGGT antibody (PCA: from 0.7 ± 0.6 to 0.3 ± 0.3, n=11, p<0.001, TFαL: from 89 ± 39 to 193 ± 65, n=6, p<0.001). HG amplified GGT-induced TF stimulation (PCA: from 0.4 ± 0.3 to 4.3 ± 3, n=7, p<0.001, mRNA: from 0.05 ± 0.04 to 0.5 ± 0.3, n=8, p<0.001, BAY-11-7082 (NG: from 0.2 ± 0.1 to 0.08 ± 0.1, n=7, HG: from 4.3 ± 3 to 0.2 ± 0.1, n=4, p<0.001) and NAC (NG: from 0.3 ± 0.1 to 0.08 ± 0.1, n=7, HG: from 3.9 ± 2.8 to 0.6 ± 0.2, n<0.001) abolished GGT-induced PCA both NG and HG conditions.

Conclusions: GGT stimulates directly TF expression in PBMCs through a NFκb-mediated mechanism and HG amplifies that effect, potentially contributing to the atherothrombotic risk conferred by higher GGT levels, more markedly in diabetic patients.