11 Acute hyperglycemia abolishes cardioprotection by remote ischemic preconditioning
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Background: Remote ischemic preconditioning (RIPerC) has a promising therapeutic value to improve the 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 to 25 mmol/L throughout the experimental protocol. NG rats received mannitol infusion as 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 immunofluorescence 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 46.27 ± 5.31% vs. NG + RIPerC 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 LC3B/LC3II ratio decreased and phosphorylated S6 increased possibly via the phosphorylation of Akt. Furthermore, acute hyperglycemia significantly elevated the nitrative stress in the heart (0.07 ± 0.01 vs. 0.50 ± 0.04 μmol g⁻¹ 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.

12 Deregulation of thioredoxin system contributes to monocyte dysfunction in diabetes mellitus: Implications for impaired arteriogenesis in type 2 diabetic patients
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Purpose: Arteriogenesis is a process encompassing the growth of pre-existing collateral blood vessels to form functional arteries. Monocytes play a positive role in this process. Diabetes mellitus (DM) led to significant downregulation of VEGFR1 signal transduction in monocytes. Understanding the molecular mechanisms that contribute to monocyte dysfunction in diabetes is important for the development of therapeutic strategies to improve arterialization of diabetic tissues. Therefore, the present study was aimed to determine the role of thioredoxin (Trx) system in monocyte dysfunction in diabetes.
Methods: Monocytes from diabetic patients or non-diabetics and monocytes from db/db mice or Wt mice were used to inhibit Trx and a Trx Mimetic Peptide (TMP) was used to study the effects of Trx.

Conclusions: Deregulated Trx system contributes to higher oxidative stress-related deregulation of PT activity in hyperglycemic monocytes. Improving Trx activity in diabetic monocytes ex vivo restored monocyte dysfunction in an ex vivo assay. Daily administration of TMP to db/db mice resulted in significantly improved hindlimb re-perfusion compared to db/db mice receiving placebo.

13 High glucose increases gamma-glutamyltransferase-induced tissue factor expression in human peripheral blood mononuclear cells
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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 insofar.

Aims: To assess the effect of an enzymatically inactive human recombinant (hr) GGT to TF antigen.

Methods: PBMCs obtained from healthy donors (discontinuous Ficoll/Hystopaque density gradient) were incubated with hrGGT (0.5ug/ml) either alone or with anti-hrGGT, a specific polyclonal antibodies (2-5ug/ml). Because of the pivotal role played by NFB, a redox-sensitive transcription factor encoding TF, we also evaluated the effect NF-κB inhibition by BAY-11-7082 (10-5M) and N-acetylcyctein (NAC) (10-5M), an antioxidant. TF PCA (1-stage clotting assay, arbitrary units), ag (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 0.08 ± 0.07 to 0.37 ± 0.3, n=14, p<0.01), ag (from 85 ± 59 to 536 ± 32, n=13, p<0.001) and mRNA (from 0.06 ± 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<0.01, TFG from 49 ± 394 to 193 ± 65, n=6, p<0.001). HG amplified GGT-induced TF stimulation (PCA: from 0.4 ± 0.3 to 4 ± 3, n=27, p<0.001, mRNA: from 0.05 ± 0.04 to 0.5 ± 0.35, 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 0.23±0.6, n=6, p<0.001) abolished GGT-induced PCA both NG and HG conditions.

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