

Organic nitrates in an experimental model of *Diabetes mellitus type 1*: Effects of pentaerythryl tetranitrate and isosorbide-5-mononitrate*

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Background

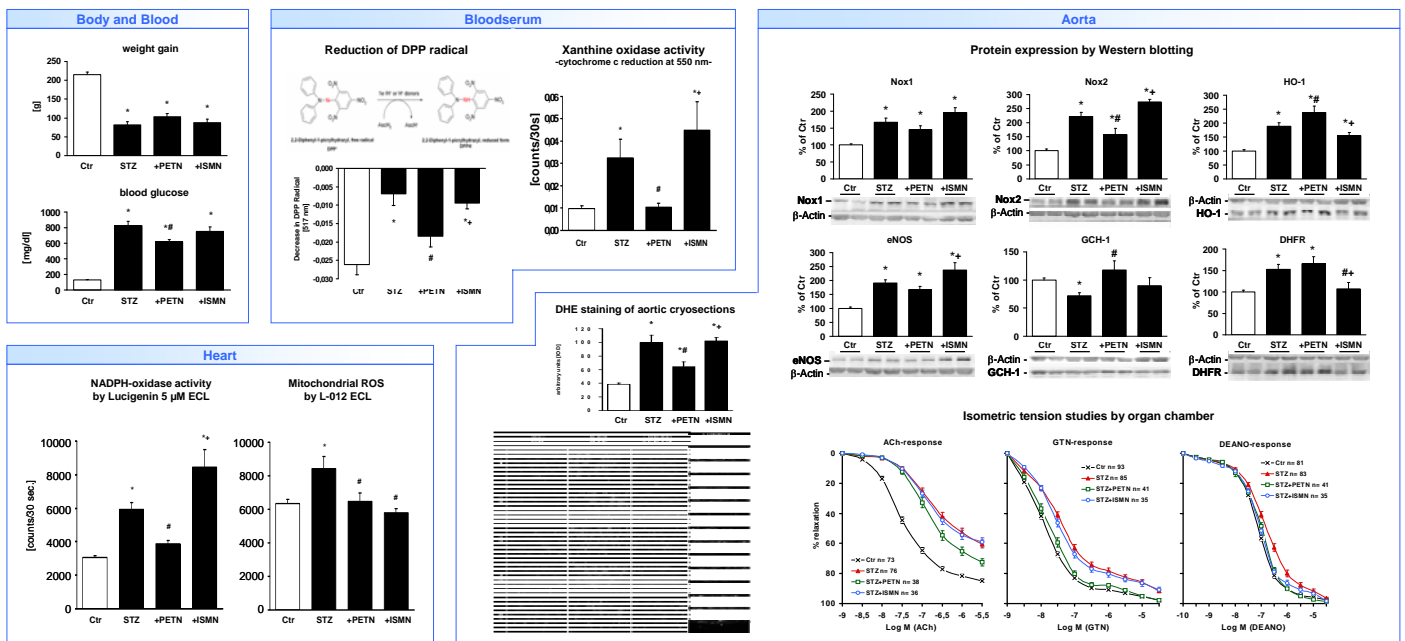
Cardiovascular complications in patients with diabetes mellitus are associated with increased oxidative stress. In contrast to other organic nitrates pentaerythryl tetranitrate (PETN)-treatment induces neither nitrate tolerance nor cross-tolerance, which has been attributed to the induction of the expression of antioxidants like heme oxygenase-1 (HO-1) and Ferritin and by eNOS-cofactor repairing (by GTP-CH-1 and DHFR) mechanisms⁽¹⁾. With the present study we tested in a rat model of streptozotocin (STZ) induced Diabetes mellitus, whether chronic treatment with PETN will preserve it's beneficial effects compared to effects of chronic treatment with Isosorbide-5-mononitrate (ISMN) in diabetes-associated vascular oxidative stress and dysfunction.

Methods

Diabetes was induced by a single i.v. injection of STZ (60 mg/kg) in male wistar rats (220-250 g). PETN and ISMN therapy started 7 d after STZ-injection by a special chow (dose: 15 mg/kg/d and 75 mg/kg/d, respectively). The rats were sacrificed after 8 weeks and diabetes was diagnosed by 3-4-fold increased blood glucose levels and significant diminished weight gain in the STZ-treated group. A small collective of STZ-rats was treated with insulin (2.5 U/d) for 2 weeks before sacrifice. Reactive oxygen species (ROS) were detected by chemiluminescence or fluorescent microtopography, protein expression was measured by Western blotting and endothelial and smooth muscle function was assessed by isometric tension studies. Additionally the antioxidative capacity and xanthine oxidase activity of blood serum was measured photometrical by reduction of the DPP-radical at 517 nm and cytochrome c reduction at 550 nm, respectively.

STZ + Nitrates

P<0.05: * vs. Ctr; # vs. STZ; + vs. STZ+PETN



Results

After 8 weeks STZ-treated rats showed a dramatical increase in blood glucose levels, decrease in weight gain, increased vascular and cardiac (mitochondria, NADPH oxidase activity) ROS production, decreased antioxidative capacity of serum and impaired endothelial and smooth muscle function. PETN therapy improved almost all parameters whereas ISMN showed no protective effects. Insulin normalized all parameters completely proving that STZ-induced vascular dysfunction strictly depends on insulin levels but not on unspecific toxicity of the compound.

Discussion

In diabetic rats, PETN showed pronounced antioxidative effects and preserved it's beneficial effects on vascular function. In contrast, the mononitrate ISMN had no protective effects in accordance with previous studies⁽¹⁾. Insulin completely normalized all tested parameters and thereby identified the underlying mechanism of cardiovascular dysfunction in STZ-induced diabetes to strictly depend on insulin levels highlighting the clinical importance of this experimental animal model.

⁽¹⁾Schuhmacher et al.: Pentaerythryl tetranitrate improves angiotensin II induced vascular dysfunction by induction of heme oxygenase-1; *Hypertension* 2010

STZ + Insulin

P<0.05: * vs. Ctr; # vs. STZ

