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3 **V1661 - Pentaerithryl tetranitrate improves angiotensin-II induced vascular oxidative stress**
4 **and vascular dysfunction via induction of heme oxygenase-1**

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11 The organic nitrate pentaerithryl tetranitrate (PETN)-treatment is devoid of nitrate tolerance, which
12 has been attributed to the induction of the antioxidant enzyme heme oxygenase-1 (HO-1). With the
13 present study we tested, whether chronic treatment with PETN can improve angiotensin-II (AT-II)-
14 induced vascular oxidative stress and dysfunction. In contrast to isosorbide mononitrate (ISMN,
15 75mg/kg/d/7d), treatment with PETN (15mg/kg/d/7d) improved impaired endothelial and smooth
16 muscle function and normalized vascular and cardiac ROS production (mitochondria, NADPH oxidase
17 activity and uncoupled endothelial nitric oxide synthase [eNOS]) as assessed by dihydroethidine
18 (DHE)-staining, lucigenin-enhanced chemiluminescence and quantitative HPLC of DHE-oxidation
19 products in AT-II (1mg/kg/d/7d) treated rats. The antioxidant features of PETN were recapitulated in
20 spontaneously hypertensive rats. In addition to increase in HO-1 protein expression, PETN but not
21 ISMN augmented aortic protein levels of the tetrahydrobiopterin-synthesizing enzymes GTP-
22 cyclohydrolase-I and dihydrofolate reductase in AT-II-treated rats, thereby preventing eNOS
23 uncoupling. Knockout of HO-1 completely abolished the beneficial effects of PETN in AT-II treated
24 mice, whereas HO-1 induction by hemin (25mg/kg) mimicked the effect of PETN. Improvement of
25 vascular function in this particular model of arterial hypertension by PETN largely depends on the
26 induction of the antioxidant enzyme HO-1 and identifies PETN as the only organic nitrate being able to
27 improve rather than to worsen endothelial function.

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