Endothelin-1 (ET-1) has been shown to have an important role in diabetic nephropathy (DN). Here we investigated the contribution of endothelial cell-derived ET-1 to the changes in renal phenotype of diabetic mice. Therefore, we induced type 1 diabetes in vascular endothelial cell-specific ET-1 knockout (VEETKO) mice and their wild type (WT) littermates by streptozotocin injection (i.p. 50 mg/kg/day, five consecutive days). After ten and 22 weeks of diabetes, we observed an increase of food and water intake, urine volume and creatinine clearance in both genotypes compared to non-diabetic mice. The renal cortical expression of ET-1 mRNA was not significantly activated by diabetes. Nevertheless, VEETKO mice showed only about half of ET-1 mRNA expression compared to WT mice. Though, there were no significant differences in the renal function including albumin and protein excretion between the genotypes. Based on hematocrit measurements, neither diabetes nor ET-1 deficiency had an impact on fluid retention. After ten weeks of diabetes, systolic blood pressure measured by tail-cuff method decreased in WT mice. After 22 weeks, heart rate and systolic and diastolic blood pressure were similar between all groups. At baseline the kidneys of VEETKO mice were significantly heavier (+15%) compared to WT mice but this gap was not observed in diabetic condition. In contrast to previously presented data, in this model of type 1 diabetes we are not able to confirm the pivotal role of endothelial cell derived ET in the development of DN.


Absence of ETA receptors on podocytes is not antialbuminuric in diabetic mice
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Background: Endothelin receptor antagonists reduce albuminuria in diabetic patients. However, adverse effects related to fluid retention and attributed to the blocking of the tubular endothelin receptors prevent the use of ERA clinically. The endothelin A (ETA) receptors on podocytes might be implicated in albuminuria during diabetes. We hypothesized that the suppression of the ETA receptors on the podocytes may reduce albuminuria without affecting the tubular functions. Methods and results: To address this question, we generated podocyte specific ETA deficient mice using ETA floxed mice mated with mice expressing the Cre recombinase under the control of the nephrin gene (PodoETAKO mice). We induced type-1 diabetes in seven-week old male PodoETAKO mice and their wild type (WT) littermates by streptozotocin injection (i.p. 50 mg/kg/day, five consecutive days). A set of animals were treated with macitentan, a dual ETA/ETB antagonist (25 mg/kg/day, orally, mixed with food). The hyperglycemic mice developed glomerular hyperfiltration, renal hypertrophy, reduced serum creatinine levels, albuminuria, tubular injury, glomerular hypertrophy and inflammation. After 20 weeks of diabetes, the absence of ETA receptors on podocytes had no effect on these parameters. Macitentan treatment however reduced albuminuria and restored serum creatinine levels in wild type mice. Interestingly, the effects of macitentan were diminished in PodoETAKO mice. Similarly, macitentan increased podocyte number per glomerulus (WT-1 positive cells) and glomerulus size in WT but not in PodoETAKO mice. Neither ETA deficiency nor macitentan treatment increased water retention measured as free water clearance. Conclusion: In contrast to systemic dual ETA/ETB receptor blockade, the suppression of the ETA receptors on podocytes is not antialbuminuric in diabetic mice.


ET-1 plasma levels, choroidal thickness and multifocal electrotoretinogram in retinitis pigmentosa
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Retinitis pigmentosa (RP) is an inherited retinal disorder characterized by bone spicul pigment in the retina, attenuated retinal blood vessels and a pale, waxy optic nerve head with head with early visual field contraction and decrease of the electrotoretinogram (ERG). Retinal hemodynamic impairment is still present in early stages of RP and various hypotheses have been advanced as to a cause. We studied with multifocal electrotoretinogram (mERG) of the macula and optical coherence tomography (OCT) of the choroid 24 patients, 14 males and 10 females, aged 63–45 yrs. (mean 55 ± 7 yrs.) and affected by simplex RP. The patients had a visual acuity of 0.1 log MAR with a mean defect (MD) of the visual field of −12.32 ± 8.48 dB, a pattern standard deviation index (PSD) of 6.09 ± 4.22 dB and a b-wave electrotoretinogram (ERG) amplitude of 45.08 ± 8.24 &micronuV. An increase of endothelin-1 (ET-1) plasma levels was found: 2.143 ± 0.258 pg/ml vs. 1.219 ± 0.236 pg/ml in non-RP controls (p < 0.002). The choroidal thickness was 226.75 ± 76.37 μm vs. 303.9 ± 39.87 μm (p < 0.002) in normal controls. The Spearman’s correlation test highlighted that the decrease of choroidal thickness (r = −0.702; p < 0.023) and the increase of time latency in the rings 2 (r = −0.669; p < 0.034) and 3 (r = −0.883; p < 0.007) of mERG were related to the increase of ET-1 plasma levels. It is thought that an increase in ET-1 in our RP could lead to a vasoconstriction in the choroidal vessels and worsening the abiotropic process of the macular photoreceptors with increase of the conduction implicit time.


Clinical value of plasma pentraxin 3 levels for predicting cardiac troponin elevation after percutaneous coronary intervention
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Background: Percutaneous coronary intervention (PCI) is often complicated by post-procedural myocardial necrosis as manifested by elevated cardiac troponin. Plasma pentraxin 3 (PTX3) levels are increased in patients with arterial inflammation, especially unstable angina pectoris (AP). The study tested whether plasma PTX3 levels can predict post-PCI cardiac troponin T (TnT) elevation. Methods: We evaluated 94 consecutive patients with AP of normal pre-PCI TnT levels who underwent PCI. Pre-PCI virtual histology-intravascular ultrasound was performed to assess culprit plaque composition.