The ET-1 / Endothelin A receptor axis for the integrity of the glomerular filtration barrier under diabetes in mice

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ET-1 antagonism may be beneficial against proteinuric diseases, like diabetic nephropathy (DN). Which cells should be targeted and whether dual or receptor specific antagonists should be used remain open questions. An important feature of DN is the dysfunction of podocytes. Several *in vitro* studies revealed the detrimental role of Endothelin A receptor (ETA) in the pathology of these cells under hyperglycemia. Using vascular endothelium specific ET-1 knock-out mice, we showed that ET-1 from endothelial cells impacts negatively podocyte structure under diabetes. Importantly, these mice develop less albuminuria than wild-type mice.

To reveal the differential role of ET receptors in these processes and particularly to address the clinical potential of glomerular ETA blockade, we generated podocyte specific ETA knock-out (PodETAKO) mice. To achieve this, we bred mice carrying a floxed ETA gene with mice expressing the crerecombinase under the control of the promotor of the gene coding for podocin (both lines have already been published). The specific recombination of ETA in the renal cortex has been confirmed by polymerase chain reaction. At the age of seven weeks, the male PodETAKO mice (n=12) did not differ from wild-type (WT) mice (n=18) in general appearance, body weight, and systolic and diastolic blood pressure measured by tail cuff method. Metabolic cage experiment revealed that food and water intake, urine volume, protein, albumin and creatinine excretion was similar between both genotypes. After immunofluorescent staining (PodETAKO n=8, WT n=4), we could not observed changes in the intensity and distribution of nephrin. Based on creatinine serum level measured by mass spectrometry, creatinine urine level measured by ELISA, and urine flow, we have calculated glomerular filtration rate (GFR). At baseline, absence of ETA on podocytes had no statistical influence on GFR (PodETAKO: 150.7±17.8 µL/min (n=10), WT: 180.2±14.6 µL/min (n=18)).

In conclusion, ETA on podocytes is not required for normal kidney function in young mice. Nevertheless, we believe that podocyte ETA plays a critical role in the development of DN. We have induced diabetes in our new model using streptozotocin (i.p., 50mg/kg, five consecutive days). The results of this experiment should clarify the role of ETA on podocytes for the integrity of the glomerular filtration barrier during DN. Finally, this model will help answering whether specific blockade of ETA in the glomerulus represents a rational approach for the treatment of proteinuric diseases.