Regulation Renal Salt and Water Absorption by the Collecting Duct Transcription Factor, PPARgamma

Matthew D. Breyer

Eli Liilly and Company Indianapolis IN, USA

Thiazolidinediones (TZDs) are widely used to treat type 2 diabetes mellitus; however their use is complicated by systemic fluid retention. Along the nephron, the pharmacological target of TZDs, peroxisome proliferator- activated receptor-gamma (PPARgamma), is most abundant in the collecting duct. Studies of mice weight gain occurring within 48-96 hours of initiation of TZD treatment and that this early weight gain is from increased total body water. The fluid retention was blocked by the collecting duct-specific diuretic amiloride and was also prevented by genetic deletion of PPARgamma from the collecting duct, using PPARgamma (flox/flox) mice. Deletion of collecting duct PPARgamma decreased renal Na (+) avidity and increased plasma aldosterone. Treating cultured collecting ducts with TZDs increased amiloride-sensitive Na (+) absorption and Scnn1g mRNA (encoding the epithelial Na (+) channel ENaC gamma) expression withing one hour of treatment. This increase in ENaCgamma was dependent on PPARgamma-expression and blocked by a PPARgamma antagonist. Furthermore chromatin immunoprecipitation (ChIP) showed association of PPARgamma with the Scnn1g gene. These studies identify Scnn1g as a PPARgamma target gene in the collecting duct. Activation of this pathway appears to mediates fluid retention associated with TZDs, and suggests amiloride like drugs might provide a specific therapy for this condition.