

## Role of Tonicity Responsive Enhancer Binding Protein (TonEBP) in Cyclosporine-induced Urinary Concentrating Defect

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**Purpose :** Long-term treatment of cyclosporine A (CsA) leads to down regulation of aquaporins and urea transporters in the kidney in association with a defect in urine concentration. In this study, we evaluated how urine concentrating machinery regulates during CsA treatment. To investigate this, we examine the followings. Regulation of sodium transporter and tonicity responsive enhancer binding protein (TonEBP) in CsA treated rat kidney, whether the tonicity of the renal medulla is lowered by chronic treatment of CsA.

**Methods :** Rats were received a daily subcutaneous injection of CsA at a dose of 15 mg/kg for 1 or 4 weeks. Osmotic minipumps delivered 0.1  $\mu\text{g/h}$  of DDAVP to Vehicle or CsA treated rats for the last 7 days of the experimental period.

**Results :** CsA treatment reduced expression of NKCC2, NCC, Na, K, ATPase, and TonEBP (including its target genes; SMIT, AR, BGT1, UT-A, AQP2,) in 4 weeks treated rat kidney. This was correlated with urine osmolality and volume. Immunohistochemical analysis shows reduced immunoreactivity of TonEBP in the IMCD. Consistent with decreased activity of TonEBP, expression of SMIT, AR, BGT1, UT-A2, AQP2, decreased in CsA treatment for 4 weeks. However, when hypotonic renal medulla by CsA was changed to hypertonic condition by dDAVP administration, TonEBP activity was increased in the renal medulla concomitant with upregulation of its target genes UT-A2, AQP2 but not UT-A1, SMIT, AR, BGT1.

**Conclusion :** We suggested downregulation of sodium transporters and TonEBP may contribute urine concentrating capacity on chronic CsA nephropathy.