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Hydrogen Sulfide Upregulates Renal AQP2 Protein Expression and Promotes Urine Concentration

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Increasing evidence supports the important role of H2S in renal physiology and the pathogenesis of kidney injury. Whether H2S regulates water metabolism in the kidney and the potential mechanism are still unknown. The present study was conducted to determine the role of H2S in urine concentration. Inhibition of both cystathionine-γ-lyase (CSE) and cystathionine-β-synthase (CBS), two major enzymes for endogenous H2S production, with propargylglycine (PPG) and amino-oxyacetate (AOAA), respectively, caused increased urine output and reduced urine osmolality in mice, which was associated with decreased expression of aquaporin-2 (AQP2) in the renal inner medulla. Mice treated with both PPG and AOAA developed a urine concentration defect in response to dehydration, which was accompanied by reduced AQP2 protein expression. Inhibition of CSE alone was associated with a mild decrease in AQP2 protein level in the renal medulla of heterozygous CBS mice. GYY4137, a slow H2S donor, markedly improved urine concentrating ability and prevented the downregulation of renal AQP2 protein expression in mice with lithium-induced nephrogenic diabetes insipidus (NDI). GYY4137 significantly increased cAMP levels in cell lysates prepared from IMCD suspensions. AQP2 protein expression was also upregulated, which was inhibited significantly by the adenylate cyclase inhibitor MDL12330A or the PKA inhibitor H89, but not the V2R antagonist tolvaptan. Inhibition of endogenous H2S production impaired urine concentration in mice whereas an exogenous H2S donor improved urine concentrating ability in lithium-induced NDI by increasing AQP2 expression in the collecting duct principal cells. H2S upregulated AQP2 protein expression, probably via the cA MP-PKA pathway.