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Binding of vasopressin to its type-2 receptor in renal collecting ducts induces cAMP signaling, transcription and translocation of aquaporin-2 (AQP2) water channels to the plasma membrane and water reabsorption from the pro-urine. Demeclocycline is currently used to treat hyponatremia in patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Demeclocycline's mechanism of action, which is poorly understood, is studied here. In mouse cortical collecting duct (mpkCCD) cells, which exhibit dDAVP-dependent expression of endogenous AQP2, demeclocycline decreased AQP2 abundance and gene transcription, but not its protein stability. Demeclocycline did not affect V2R localization, but decreased dDAVP-induced cAMP generation and adenylate cyclase 3 and 5/6 abundances. Addition of exogenous cAMP partially corrected the demeclocycline effect. As in patients, demeclocycline increased urine volume, decreased urine osmolality and reverted hyponatremia in an SIADH rat model. AQP2 and adenylate cyclase 5/6 abundances were reduced in the inner medulla, but increased in the cortex and outer medulla, in the absence of any sign of toxicity. In conclusion, our in vitro and in vivo data indicate that demeclocycline mainly attenuates hyponatremia in SIADH by reducing adenylate cyclase 5/6 expression, and consequently cAMP generation, AQP2 gene transcription and AQP2 abundance in the renal inner medulla, coinciding with a reduced vasopressin-escape response in the other collecting duct segments.

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