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Haloperidol and sertraline activate AQP2 via cAMP/PKA signaling in the inner medullary collecting duct

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Objectives: Antipsychotics or antidepressants may be associated with hyponatremia, but how they induce water retention in the kidney remains elusive. Previous literatures have postulated that they may increase vasopressin production in the hypothalamus. In this study, we tested the other possibility of drug-induced nephrogenic syndrome of inappropriate antidiuresis (NSIAD) using haloperidol and sertraline.

Methods: Haloperidol (5 μM) or sertraline (1 μM) were treated in inner medullary collecting duct (IMCD) suspensions and primary cultured IMCD cells prepared from male Sprague-Dawley rats. Intracellular cAMP levels were measured using a competitive enzyme immunoassay kit in IMCD suspensions. Aquaporin-2 (AQP2) protein abundance and localization were estimated by immunoblot analysis and immunofluorescence microscopy, respectively. The mRNA levels of vasopressin-2 receptor (V2R) and AQP2 were measured by qPCR analysis. The responses were compared when dDAVP (10 nM), tolvaptan (100 nM), and a PKA inhibitor H89 (30 μM) were treated.

Results: In IMCD suspensions, cAMP production was significantly increased by haloperidol or sertraline but was blocked by tolvaptan cotreatment. In primary cultured IMCD cells, haloperidol or sertraline treatment for 30 min induced significant increases in AQP2 and pS256-AQP2 protein and a significant decrease in pS261-AQP2. Notably, these responses were reversed by tolvaptan or H89 cotreatment. Immunofluorescence microscopy demonstrated that membrane trafficking of AQP2 was induced by haloperidol and sertraline and was blocked by tolvaptan or H89 cotreatment. Furthermore, V2R and AQP2 mRNA were significantly upregulated by haloperidol or sertraline treatment.

Conclusions: In the rat IMCD, both haloperidol and sertraline activate AQP2 via V2R-cAMP-PKA signaling in the absence of vasopressin stimulation. The vasopressin-like action on the kidney appears to induce upreguation of AQP2 transcription and phosphorylation at serine 256 in IMCD.