Abstract Type : Oral
Abstract Submission No. : 1733

Tolvaptan reverses duloxetine-induced antidiuresis in lithium-induced nephrogenic diabetes insipidus

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Objectives: Antidepressants are an important cause of drug-induced hyponatremia, which disturbs the continuation of medication. Tolvaptan is useful for correcting hyponatremia caused by syndrome of inappropriate antidiuresis, but its effect on drug-induced hyponatremia is unknown.

Methods: Male Sprague-Dawley rats were used to determine the effects of duloxetine treatment in lithium-induced nephrogenic diabetes insipidus (Li-NDI) and to evaluate whether the results were reversed by tolvaptan co-treatment. To induce Li-NDI, lithium chloride (40 mmol lithium/kg dry food) was given for 2 weeks. Duloxetine (50 mg/kg/d) and tolvaptan (10 mg/kg/d) were additionally provided in food to test their respective effects for the same period. At the end of each animal experiment, kidneys were harvested to measure cAMP, vasopressin-2 receptor (V2R), cAMP-responsive element binding protein 1 (CREB-1), aquaporin-2 (AQP2), and prostaglandin E2 (PGE2) levels.

Results: Water diuresis was induced in the Li-NDI rats, and duloxetine treatment reduced polyuria in association with increased urine osmolality. Reduced total AQP2, AQP2 phosphorylation at serine 256, and CREB-1 phosphorylation in Li-NDI rats were blocked by duloxetine treatment. V2R mRNA level was also reduced in Li-NDI rats and restored by duloxetine treatment. In the subsequent experiment, the reduced water diuresis in duloxetine-treated Li-NDI rats was reversed by tolvaptan co-treatment. Tolvaptan co-treatment also reversed the changes in AQP2 protein and CREB-1 phosphorylation in the renal cortex and medulla. The reduced cAMP in Li-NDI rat kidneys was increased by duloxetine treatment, and that increase was reversed by tolvaptan co-treatment. However, elevated PGE2 in Li-NDI rat kidneys was not changed by either duloxetine alone or tolvaptan co-treatment.

Conclusions: In Li-NDI, antidiuresis was caused by duloxetine and reversed by tolvaptan co-treatment via alterations in the V2R-cAMP-AQP2 pathway. These findings could underlie the mechanism of duloxetine-induced hyponatremia and suggest the potential usefulness of tolvaptan in treating drug-induced hyponatremia.