No. 2232

Fluid Homeostasis by Sodium-Glucose Cotransporter 2 Inhibition: Mechanism of Fluid Intake and Vasopressin Secretion

Takahiro Masuda[1], Shigeaki Muto[1], Masahide Yoshida[2], Volker Vallon[3], Daisuke Nagata[1]

[1] Division of Nephrology, Department of Internal Medicine, Jichi Medical University,
[2] Division of Brain and Neurophysiology, Department of Physiology, Jichi Medical University,
[3] Division of Nephrology and Hypertension, Departments of Medicine and Pharmacology, University of California-San Diego, USA

Summary

Na^+-glucose co-transporter 2 (SGLT2) inhibitors are antihyperglycemic agents that suppress glucose reabsorption by inhibiting SGLT2 in the early proximal renal tubules; SGLT2 inhibitors cause mild natriuresis and osmotic diuresis with glucose, as previously reported in diabetic rats Vasopressin maintains fluid volume by promoting water uptake and reabsorption in the collecting ducts, as previously reported in diabetic rats. Loop diuretics, on the other hand, are commonly used diuretics for the treatment of fluid retention, but they induce renal dysfunction related to hypovolemia. Therefore, we investigated 1) whether SGLT2 inhibitors and loop diuretics activate similar mechanisms of fluid homeostasis and 2) what factors are associated with these mechanisms.

Non-diabetic male Sprague-Dawley rats received daily oral doses of vehicle, the SGLT2 inhibitor ipragliflozin (5 mg/kg) or the loop diuretic furosemide (50 mg/kg), and were monitored for 2 or 7 days in a metabolic cage. Ipragliflozin and furosemide similarly increased urine output on day 2. This was associated with increased water intake, serum Na^+ and Cl^- concentration, urinary vasopressin excretion, and soluble-free water reabsorption in response to ipragliflozin but not furosemide. Ipragliflozin maintained fluid balance (water intake - urine output) on day 2 and total body water as measured by bioimpedance spectroscopy and serum creatinine on day 7. In contrast, furosemide decreased fluid balance on day 2, decreased total body water on day 7, and increased serum creatinine.

In conclusion, the osmotic diuresis of the SGLT2 inhibitor increased serum Na^+ and Cl^-concentration and the vasopressin-related stimulation of fluid intake and renal water reabsorption maintained fluid balance, whereas the loop diuretic did not increase serum Na^+ and Cl^- concentration and did not stimulate the compensatory vasopressin system. These data suggest the differences in vasopressin and fluid homeostatic responses between SGLT2 inhibitor and loop diuretic, and the change in serum Na^+ and Cl^- concentration as a determinant for the differences.