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Sodium-phosphate cotransporter mediates reabsorption of lithium in rat kidney

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ABSTRACT

Lithium, used for the treatment of bipolar disorders, is reabsorbed via sodium-transport system in the proximal tubule. This step causes intra-/inter-individual difference of lithium disposition, and it has not been unclear which transporter contributes. In this study, we examined effect of foscarnet and parathyroid hormone (PTH), inactivators for sodium-phosphate cotransporter, and phlorizin, a typical inhibitor for sodium-glucose cotransporter, on the disposition of lithium in rats. Their intravenous administration stimulated urinary excretion of phosphate or glucose. After the intravenous injection of lithium chloride as a bolus, plasma concentration of lithium decreased time-dependently. The renal clearance of lithium was calculated to be 0.740 ml/min/kg in control rats, and this was 26.7% of creatinine clearance. Foscarnet and PTH significantly increased the renal clearance of lithium and its ratio to creatinine clearance, suggesting that they prevented the reabsorption of lithium. No effect of phlorizin on the renal handling of lithium was recognized. In control rats, the renal clearance of lithium showed a strong correlation with the renal excretion rate of phosphate, compared with creatinine clearance. These findings suggest that sodium-phosphate cotransporter reabsorbs lithium in the rat kidney. Furthermore, its contribution was estimated to be more than 65.9% in the lithium reabsorption. And, this study raised the possibility that therapeutic outcome of lithium is related with the functional expression of sodium-phosphate cotransporter in the kidney.

Introduction

Lithium is effective for the treatment and prophylaxis of bipolar disorder. Because its therapeutic index is narrow, monitoring of plasma lithium concentration is required [1,2]. Now, many clinicians regard steady-state plasma levels of 0.6–1.2 mM as optimal for the maintenance treatment of the disorders, and of 0.8–1.5 mM as ideal for the acute management [2]. In patients with the lithium plasma levels exceeding 1.5 mM, symptoms including lethargy, drowsiness, muscular weakness, nausea, confusion, dysarthria, nystagmus, increased deep tendon reflexes, seizure, syncope and impaired renal function are exhibited [1,2]. In addition, lithium interacts with various drugs [1,2]. So, it is accepted as one of the agents that we pay scrupulous attention, when dosing it.

Clinically, lithium is administered orally, and its gastrointestinal absorption is rapid and almost complete. Almost lithium administered is excreted into urine, and condition of the kidney and renal handling of lithium are closely correlated with the therapeutic outcome. The protein binding of lithium in plasma is negligible, so lithium is freely filtered through glomeruli [1]. Because lithium clearance is usually 25% of creatinine clearance (C_{cr}), reabsorption plays an important role in its renal handling [2]. And, it has been suggested that the proximal tubule is the main site where lithium filtered is reabsorbed [3,4].

In the proximal tubule, more than 67% of sodium after the glomerular filtration are reabsorbed, and sodium-hydrogen exchanger NHE3, expressed in the brush-border membrane of proximal epithelial cells, plays a predominant role [5]. In addition, many kinds of transporters mediate uptake of each substrate including glucose, amino acids, dicarboxylic acids, sulfate, carnitine, ascorbic acid, and phosphate, using sodium gradient [6–11]. It is considered that these transporters are involved in the reabsorption of lithium in addition to sodium, but it has not been

Abbreviations: PTH, parathyroid hormone; C_{cr}, creatinine clearance; P_{cr}, plasma creatinine concentration; CL_r, renal clearance; AUC_{60}, area under the plasma concentration–time curve of lithium until 60 min.

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Table 1
Urinary excretion of phosphate and glucose in rats administered with foscarnet, PTH and phlorizin.

Parameter	Control	LD foscarnet	HD foscarnet	PTH	Phlorizin
N	15	10	10	12	10
Weight (g)	211 ± 2	210 ± 2	211 ± 2	206 ± 1	209 ± 2
P_{cr} (mg/dl)	0.533 ± 0.014	0.570 ± 0.016	0.561 ± 0.012	0.568 ± 0.019	0.572 ± 0.018
C_{cr} (ml/min/kg)	2.77 ± 0.11	2.64 ± 0.11	3.21 ± 0.21	2.73 ± 0.09	3.01 ± 0.21
Phosphate (mg/60 min/kg)	2.19 ± 0.36	5.00 ± 0.36**	7.67 ± 0.80***,†	6.05 ± 0.57***	N.D.
Glucose (mg/60 min/kg)	24.3 ± 4.2	N.D.	N.D.	N.D.	160 ± 21***

Each parameter represents the mean ± SE. P_{cr}: plasma creatinine concentration; C_{cr}: creatinine clearance; N.D.: not determined.
** $P < 0.01$, significantly different from control.
*** $P < 0.001$, significantly different from control.
† $P < 0.05$, significantly different from LD foscarnet.

elucidated which transporter works for the lithium transport after the glomerular filtration. The purpose of this study is to examine the contribution of sodium-phosphate cotransporter NaPi and sodium-glucose cotransporter SGLT in the lithium handling in the rat kidney. Here, we administered their inactivators, foscarnet and parathyroid hormone (PTH) for NaPi, and phlorizin for SGLT to rats, and evaluated their effects on the pharmacokinetics of lithium.

Materials and method

Materials

Lithium chloride and mannitol were purchased from Wako Pure Chemical Industries (Osaka, Japan) and Nacalai tesque (Kyoto, Japan), respectively. Foscarnet sodium and rat parathyroid hormone fragment 1–34 were obtained from Abcam (Cambridge, UK) and Sigma–Aldrich (St. Louis, MO, USA), respectively. Phlorizin was from Cayman Chemical Company (Ann Arbor, MI, USA).

Pharmacokinetic experiments of lithium using rats

Animals were treated in accordance with regulations of the Institutional Animal Use and Care Committee of School of Pharmacy, Aichi Gakuin University. Seven-week old male Wistar/ST rats were from Chubu Kagaku Shizai (Nagoya, Japan). Under the anesthesia with ethyl carbamate and α-chloralose, catheters were inserted into the femoral artery and femoral vein with polyethylene tubes (SP-31; Natsume Seisakusho, Tokyo, Japan) filled with heparin solution (50 IU/mL) for blood sampling and drug administration, respectively. Urine was collected from urinary bladder catheterized with SP-31 polyethylene tubes.

To maintain a sufficient and constant urine flow, 10% mannitol in saline was infused at 2.2 ml/h until the last blood sampling, followed by the injection as a bolus at 3 ml/kg. Foscarnet at 20 mM (LD: low dose) or 50 mM (HD: high dose), PTH at 1.64 μM and phlorizin at 30 μM were coadministered with mannitol. Lithium chloride was dissolved in saline, and was intravenously injected as a bolus at 3 mg/kg, 20 min after the start of mannitol infusion. Blood was collected 1, 2, 5, 10, 30 and 60 min after the lithium administration, and centrifuged for plasma sampling. Bladder urine samples were collected from the lithium administration to the last blood sampling.

After appropriately diluted with 0.1% nitric acid, the concentrations of lithium in plasma and urine were determined, using atomic absorption spectrometry Agilent 240Z AA (Agilent Technologies, Santa Clara, CA, USA).

The area under the plasma concentration-time curve of lithium until 60 min (AUC_{60}) was calculated with the aids of trapezoidal rule method. The renal clearance (CL_r) of lithium was obtained by dividing its urinary amount until 60 min after the lithium injection by AUC_{60}.

C_{cr}, and urinary excretion rates of phosphate and glucose

The concentrations of creatinine, phosphate and glucose in samples of the bladder urine or plasma were determined using the assay kits from Wako Pure Chemical Industries (Osaka, Japan). C_{cr}, and urinary excretion rates of phosphate and glucose were calculated.

Statistical analysis

Data were analyzed by the unpaired *t*-test or one-way analysis of variance followed by Scheffé's test using KaleidaGraph (Synergy Software, Reading, PA, USA). Differences were considered significant at $P < 0.05$.

Results

Urinary excretion of phosphate and glucose in rats administered with foscarnet, PTH and phlorizin

To inactivate NaPi and SGLT in the kidney, their depressors were intravenously administered to rats. The concentrations of phosphate and glucose in the urine were measured and their amounts excreted into urine were represented in Table 1. In control rats, 2.19 ± 0.36 mg/kg of phosphate (mean ± SE of 15 rats) were recovered into urine until 60 min after the lithium injection. In rats administered with foscarnet at 20 mM (LD foscarnet), the phosphate amount into urine was significantly enhanced ($P < 0.01$). The significant increase of its urinary content was recognized by the dosage augmentation of fosarnet to 50 mM (HD foscarnet). And, the phosphate amount was determined to be 6.05 ± 0.57 mg/60 min/kg in rats treated with PTH ($n = 10$), another inactivator of NaPi, and this was significantly greater than that in control group ($P < 0.001$). In glucose, 24.3 ± 4.2 mg/kg were recovered into urine until 60 min after the lithium administration in control group, and phlorizin significantly elevated the urinary excretion of glucose ($P < 0.001$). Accordingly, the inhibition of NaPi and SGLT in the kidney by the administration of their inactivators was recognized in this study.

Table 1 also represents plasma concentration of creatinine (P_{cr}) and C_{cr}. No significant change of them was recognized by the administration of foscarnet, PTH and phlorizin.

Effect of foscarnet and PTH on disposition of lithium

Fig. 1 shows effect of foscarnet and PTH on the disposition of lithium in rats. After its injection as a bolus, the plasma concentration of lithium decreased time-dependently. Foscarnet and PTH did not influence the plasma levels of lithium (Fig. 1A). Fig. 1B illustrates the urinary excretion of lithium. Its cumulative amount excreted into urine was increased linearly, and 5.71 ± 0.71% of lithium injected were recovered into urine until 60 min in control group. Although Scheffé's test did not detect statistical difference, it increased to 10.0 ± 1.0% of the dose in LD foscarnet group. In