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Inhibitory effect of JBP485 on renal excretion of acyclovir by the inhibition of OAT1 and OAT3

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ABSTRACT

The purpose is to investigate whether the targets of drug-drug interactions (DDIs) between JBP485 and acyclovir are OAT1 and OAT3 in kidney. Plasma concentration and accumulative urinary excretion of acyclovir in vivo, uptake of acyclovir in kidney slices and uptake of acyclovir in human (h) OAT1/ hOAT3-human embryonic kidney (HEK) 293 cells in vitro were performed to examine the effect of JBP485 on urinary excretion of acyclovir. The plasma concentration of acyclovir was increased markedly and accumulative urinary excretion and renal clearance of acyclovir were decreased significantly after intravenous administration of acyclovir in combination with JBP485. JBP485 (a substrate for OAT1 and OAT3), p-aminohippurate (PAH) (a substrate for OAT1) and benzylpenicillin (PCG) (a substrate for OAT3) could decrease the uptake of acyclovir in kidney slices and in hOAT1-/hOAT3-HEK293 cells. These results suggest that JBP485 inhibits the renal excretion of acyclovir by inhibiting renal transporters OAT1 and OAT3 in vivo and in vitro. Our results indicate the possibility of DDI between dipeptide and acyclovir.
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1. Introduction

Drug-drug interactions (DDIs) can result in severe adverse reactions when co-administration of a drug that is an inhibitor or an inducer of a drug transporter may affect the pharmacokinetics of a drug that is a substrate for that transporter. Some drugs have been withdrawn from the market due to harmful drug-drug interactions. The renal excretion of a drug involves glomerular filtration, active tubular secretion and passive reabsorption. Organic anion transporter (OAT) 1 and OAT3 are expressed on the basolateral membrane of proximal tubules and play important roles in the tubular uptake and secretion of organic compounds (Nozaki et al., 2007; Lee and Kim, 2004). The substrates of OAT1 include various compounds, such as p-aminohippurate (PAH), β-lactam antibiotics antiviral drugs, anti-inflammatory agents and endogenous organic anions, while the substrates of OAT3 include benzylpenicillin (PCG), pravastatin, cimetidine, estrone sulfate and conjugated steroids (DHEAS, E1S) (Deguchi et al., 2004; Chen et al., 2011).

Cyclo-trans-4-L-hydroxyprolyl-L-serine (JBP485) is a dipeptide (Liu et al., 2000) (Fig. 1) with obvious anti-hepatitic effects (Liu et al., 1998; Wu et al., 2008; Yang et al., 2009), and is first isolated from Laennec which is a trade name for the hydrolyzate of human placenta in Japan. Our previous studies have indicated that JBP485 is mainly excreted by the kidney and is a substrate of rat peptide transporter1 (rPept1) and rat organic anion transporter (rOats) (Zhang et al., 2010). 9-(2-Hydroxyethoxymethyl) guanine (acyclovir) is a second-generation anti-virus nucleoside analogue, which selectively inhibits members of the herpes group of DNA viruses (Elion et al., 1977). Similar to JBP485, the major route of acyclovir elimination is also renal excretion with normal renal capacity (O'Brien and Campoli-Richards, 1989) and it is transported by the OATs located on the basolateral membrane of proximal tubule epithelia (Koepsell and Endou, 2004). On the other hand, in clinic acyclovir was used to treat herpes simplex, herpes simplex keratitis, genital herpes (O'Brien and Campoli-Richards, 1989). Mentioned above, JBP485 is a dipeptide with obvious anti-hepatitic effects. It is possible for a patient suffering from hepatitis and herpes to be treated simultaneously with acyclovir and JBP485.

To determine whether co-administration of acyclovir with JBP485 can result DDI and impact the pharmacokinetics of acyclovir, and to clarify the pharmacokinetic mechanism of the DDI between acyclovir and JBP485, as well as to provide a theoretical basis for this DDI in clinical application, we constructed a LC-MS/MS method for determining acyclovir and investigated the DDI

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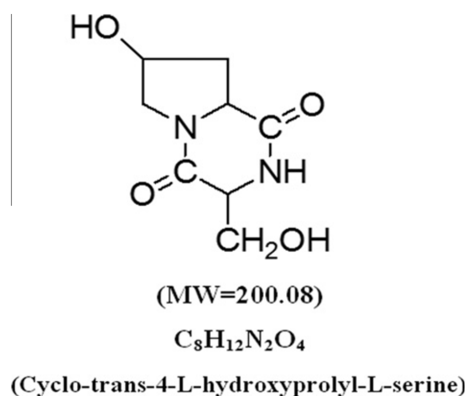

Fig. 1. Chemical structure of JBP485.

between acyclovir and JBP485 by in vivo intravenous administration, in vivo urinary excretion, in vitro kidney slices in rats and uptake studies in human hOAT1- and hOAT3-HEK293 cells. We found the changes in pharmacokinetics of acyclovir when acyclovir and JBP485 were co-administered. Our results indicated that JBP485 inhibited the renal excretion of acyclovir by the renal transporters (rOat1 and rOat3) in rats in vivo and OAT1 and OAT3 in human in vitro.

2. Methods and materials

2.1. Chemicals

Acyclovir was purchased from Hubei Tian-Guang Pharmaceutical Factory (Hubei, China). JBP485 was supplied by Japan Bioproducts Industry Co., Ltd. (Tokyo, Japan). Paracetamol (internal standard) was obtained from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). p-aminohippurate (PAH) and benzylpenicillin (PCG) were purchased from Sigma (USA). The stable transfectants of human hOAT1- and hOAT3-HEK293 cells and vector cells (mock) were provided by Professor Yuichi Sugiyama (Graduate School of Pharmaceutical Sciences, University of Tokyo, Tokyo, Japan) and Li-kun Gong (Shanghai Institute of Materia Medica, Chinese Academy of Science, Shanghai, China). All other chemicals were of analytical grade and were commercially available.

2.2. Animals

Male Wistar rats weighing 220–250 g (from the Experimental Animal Center of Dalian Medical University, Dalian, China; permit number SCXK 2008–0002) were cared for and treated in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.3. Pharmacokinetic interaction studies

We used ether to anesthetize the rats before each experiment. Acyclovir and JBP485 were soluble in normal saline or buffer solution and were administered intravenously via the jugular vein.

2.4. In vivo plasma concentration and renal excretion

We grouped the rats as follows: (1) acyclovir (30 mg/kg) alone, (2) acyclovir (30 mg/kg) + JBP485 (25 mg/kg). We collected blood samples at 1, 5, 10, 30, 60, 120, 240, 360, 480 and 600 min after intravenous administration of acyclovir alone or acyclovir with JBP485 and urine samples directly from the bladder at 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 h of administration. The concentrations of acyclovir in plasma and urine were measured by the LC-MS/MS method mentioned below. In addition, the cumulative urinary excretion and renal clearance were calculated (see Data analysis).

2.5. In vitro uptake in kidney slices

We take the renal cortex to do the kidney slices experiment. Kidney slices (0.3 mm thick with a surface area of about 0.15 cm^2) were obtained using a ZQP-86 tissue slicer (Zhixin Co., Ltd., Shanghai, China). Two slices were randomly selected and incubated in a 6-well plate with 1 ml of oxygenated incubation buffer (120 mM NaCl, 16.2 mM KCl, 1 mM $CaCl_2$, 1.2 mM $MgSO_4$, and 10 mM NaH_2PO_4/Na_2HPO_4, pH 7.5) in each well after preincubation for 3 min at 37 °C. The kidney slices were then transferred to a 24-well plate containing 1 ml of oxygenated incubation buffer and acyclovir in the presence and absence of inhibitors (JBP485, PAH and PCG). In the time-dependent experiment using acyclovir (200 μM) and inhibitors (200 μM), the uptake times were 1, 3, 5, 10 and 15 min. In the concentration-dependent experiment, the uptake time was 5 min and the concentrations of acyclovir were 10, 50, 100, 200, 500 and 1000 μM. In the inhibition experiment the uptake time was 5 min, the concentration of acyclovir was 200 μM and the concentrations of inhibitors (JBP485, PAH and PCG) were 10, 100, 1000, 10,000 and 1,00,000 μM, respectively. After incubating for the appropriate time, each slice was rapidly removed from the incubation buffer, washed in ice-cold saline, blotted on filter paper, weighed, homogenated and acyclovir concentration in homogenized kidney slices was detected using LC–MS/MS after being deproteinized by MeOH.

2.6. Uptake study using transporter-expressing cells

hOAT1-, hOAT3-HEK293 cells were established as described previously (Deguchi et al., 2004). Cells were grown in Dulbecco's modified eagle's medium supplemented with 10% fetal bovine serum, 100 U/m penicillin and 100 μg/ml streptomycin at 37 °C with 5% CO_2 and 95% humidity. Cells were seeded in 24-well plates at a density of 5×10^5 cells/well, then cells were cultured for 48 h before starting the uptake study. In uptake study, hOAT1-, hOAT3-HEK293 cells and mock cells were placed in Hank's balanced salt solution (HBSS: 118 mM NaCl, 23.8 mM $NaHCO_3$, 4.83 mM KCl, 0.96 mM KH_2PO_4, 1.20 mM $MgSO_4$, 12.50 mM HEPES, 5 mM glucose and 1.53 mM $CaCl_2$, pH 7.4). Uptake was initiated by adding HBSS (1 ml) containing acyclovir in the presence and absence of inhibitors (JBP485, PAH or PCG). After the designated times, uptake was terminated by aspirating the medium and adding ice-cold HASS. The cell lysate was analyzed by LC–MS/MS. The uptake of acyclovir in hOAT1-, hOAT3- and mock cells was measured in a time-dependent experiment (acyclovir: 200 μM, inhibitor: 200 μM), at the uptake times of 0.5, 1, 3 and 5 min; in a concentration-dependent experiment (uptake time: 3 min), at acyclovir concentrations of 10, 50, 100, 200, 500 and 1000 μM; inhibition of acyclovir (200 μM) uptake by inhibitors, the concentrations of inhibitors were 10, 100, 1000, 10,000 and 1,00,000 μM and the uptake time was 3 min.

2.7. LC–MS/MS analysis

We used a triple quadrupole mass spectrometer with electrospray ionization (ESI) on a turbo ionspray source (API 3200; Applied Biosystems, Foster City, CA, USA) coupled to a liquid chromatography system (Agilent 1200, Agilent Technology Inc., Palo Alto, CA, USA) and a C_{18} column 2.1 × 150 mm (Elite Hypersil, China) to analyze the samples. The mobile phase consisted by 10% methanol and 90% water with 0.1% formic acid, and the flow rate

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