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A Chinese herb formula decreases the monocarboxylate transporter-mediated absorption of valproic acid in rats

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ABSTRACT

Huang-Qin-Tang (HQT), a Chinese medicine prescription containing Scutellariae Radix (SR), Paeoniae Radix (PR), Glycyrrhizae Radix (GR) and JuJubae Fructus (JF), was used for the treatments of cold with symptoms of abdominalgia and diarrhea. Valproic acid (VPA) is an antiepileptic drug with narrow therapeutic window. This study investigated the effect of coadministration of HQT on the pharmacokinetics of VPA, a probe drug for monocarboxylate transporter (MCT). Rats were administered VPA alone (200.0 mg/kg) and coadministered HQT (8.0 g/kg) at 0.5 h before VPA and 1.5 h after VPA in crossover designs. In addition, the chronic effect of HQT was also evaluated by coadministration of the 7th dose at 0.5 h before VPA. The serum concentration of VPA was determined by a fluorescence polarization immunoassay. The results showed that coadministration of HQT at 0.5 h before VPA significantly decreased the AUC_{0-t} and C_{max} by 62% and 77%, respectively, whereas coadministration of HQT at 1.5 h after VPA exerted no significant influence. When the 7th dose of HQT was given at 0.5 h before VPA, the AUC_{0-t} and C_{max} of VPA were markedly decreased by 65% and 82%, respectively. Mechanism study revealed that the MCT-mediated uptake of fluorescein was inhibited by HQT and each component herbs. In conclusion, the MCT-mediated absorption of VPA was significantly decreased by concomitant administration of HQT.

Introduction

Valproic acid (VPA), 2-propylpentanoic acid (chemical structure shown in Fig. 1), is a widely used anticonvulsant and mood-stabilizing drug, but with narrow therapeutic window. Subtherapeutic level of VPA would fail to control the epileptic seizure. Conversely, supertherapeutic level of VPA would cause adverse reactions such as hepatotoxicity and teratogenicity (Bryant and Dreifuss 1996). In pharmacokinetic aspect, VPA is metabolized primarily by direct glucuronidation to form the acyl glucuronide (VPA-G) and also by β-oxidation (Davis et al. 1994; Gibbs et al. 2004). In the bloodstream, VPA is strongly bound to proteins (Palaty and Abbott 1995). Previous studies have reported that VPA (pKa = 4.56) was a substrate of monocarboxylate transporter (MCT), an influx transporter in the intestine (Utoguchi and Audus 2000; Ushigome et al. 2001).

Huang-Qin-Tang (HQT), a widely used prescription described in *Treatise on Exogenous Febrile Disease*, has been used to treat dysentery and nowadays its use has been expanded to the treatments of cold with symptoms of abdominalgia and diarrhea. HQT contains four herbs including Scutellariae Radix (SR, roots of *Scutellaria baicalensis*), Paeoniae Radix (PR, roots of *Paeonia lactiflora*) and Glycyrrhizae Radix (GR, roots of *Glycyrrhiza uralensis*) in a ratio of 3:3:1 and a few Jujubae Fructus (JF, seeds of *Ziziphus jujuba*). In regard to the complex chemical nature of HQT, SR contains many flavonoids such as baicalin, baicalein, wogonoside and wogonin; PR contains monoterpenes such as paeoniflorin and albiflorin; GR contains triterpenes such as glycyrrhizin and glycyrrhetic acid, which have been reported to have a variety of pharmacological effects such as anti-inflammatory, anti-ulcer, anti-virus, anti-tumor activities (Takagi and Harada 1969; Ikemoto et al. 2000; Aly et al. 2005; Huang et al. 2006; Fiore et al. 2008).

Among the known constituents in HQT, we hypothesize that the carboxylic acids such as baicalin, wogonoside, glycyrrhizin and glycyrrhetic acid may compete with VPA for the MCT-mediated absorption. Therefore, this study investigated the effect of HQT on the pharmacokinetics of VPA, a probe drug for MCT, in rats. In addition, cell line model was used to investigate the underlying mechanism.

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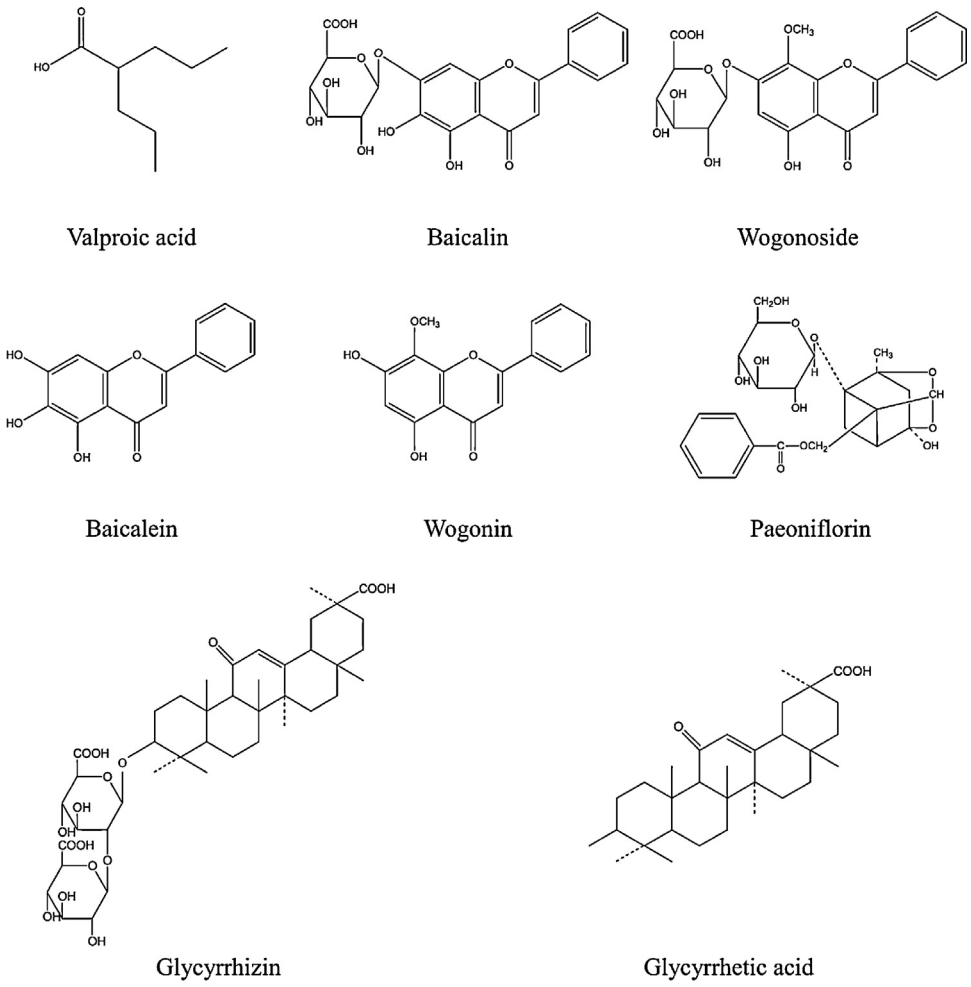

Fig. 1. Chemical structures of valproic acid, baicalin, baicalein, wogonoside, wogonin, paeoniflorin, glycyrrhizin and glycyrrhetic acid.

Materials and methods

Materials and reagents

The component crude drugs were supplied by an herbal drugstore in Taichung, Taiwan. The origins of SR (CMU-1905-5), PR (CMU-1905-9), GR (CMU-1905-7) and JF (CMU-1905-10) were identified by Dr. Yu-Chi Hou and voucher specimens were deposited in China Medical University. VPA, fluorescein, ethyl paraben, glycyrrhizin, sodium dodecyl sulfate (SDS), dimethyl sulfoxide (DMSO), calcium chloride, triton X-100, 2-morpholinoethanesulfonic acid monohydrate (MES monohydrate) and 3-(4′,5′-dimethylthiazol-2′-yl)-2,5-diphenyltetrazolium bromide (MTT) were purchased from Sigma (St. Louis, MO, USA). Dulbecco's Modified Eagle Medium (DMEM), trypsin/EDTA and Hank's Buffered Salt Solution (HBSS) were purchased from Invitrogen (Grand Island, NY, USA). Baicalin, baicalein, wogonin, paeoniflorin, salicylic acid (SA) was provided by Wako (Osaka, Japan). TDx kit was supplied by Abbott Laboratories (Abbott Park, IL, USA). Milli-Q plus water (Millipore, Bedford, MA, USA) was used throughout this study.

Preparation and characterization of HQT decoction

According to the composition ratio of each crude drug in HQT described in literature, 214.5 g of SR, 214.5 g of PR, 72.0 g of GR and a few JF were weighed to make a total of 500 g, to which 10 l of water was added and heated on a gas stove until reduced to below half volume, and then the mixture was filtered while hot with gauze. The filtrate was gently boiled until the volume reduced to less than 500 ml, then sufficient water was added to afford a concentration of 1 g/ml, and frozen at −20 °C for later use. Then, an HPLC method was developed and validated to characterize the HQT decoction. Briefly, after vortexed with MeOH and centrifuged, the supernatant (200 μl) was added 200 μl of ethyl paraben solution (25 μg/ml in methanol) as internal standard, and 20 μl was subjected to HPLC analysis. The HPLC instrumentation included one pump (LC-10ATVP; Shimadzu), an UV detector (SPD-10A; Shimadzu), an automatic injector (SIL-10A; Shimadzu), and an Apollo C18 column (4.6 mm × 250 mm, 5 μm). The mobile phase consisted of acetonitrile (A) and 0.1% phosphoric acid (B). A gradient elution was programmed as follows: A/B: 15/85 (0 min), 34/66 (20–30 min), 50/50 (40–50 min), and 15/85 (55–60 min). The detection wavelength was set at 240 nm and the flow rate was 1.0 ml/min.

Animals and drug administration

Male Sprague–Dawley rats were supplied by National Laboratory Animal Center (Taipei, Taiwan) and kept in the animal center of China Medical University (Taichung, Taiwan) in a 12 h light–dark cycle, constant temperature environment prior to study. The animal study adhered to "The Guidebook for the Care and Use of Laboratory Animals" published by the Chinese Society of Animal Science,