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Interaction of valproic acid and carbapenem antibiotics with multidrug resistance-associated proteins in rat erythrocyte membranes

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Abstract

We recently reported that the decrease in plasma valproic acid (VPA) level by carbapenem antibiotics (CPs) may partly be due to the increased erythrocyte distribution of VPA. In order to clarify the mechanisms underlying altered VPA distribution in erythrocytes, we examined the role of multidrug resistance-associated proteins (Mrps). The uptake of 2,4-dinitrophenyl-*S*-glutathione (DNP-SG), a substrate of Mrps, by inside-out vesicles (IOVs) prepared from rat erythrocytes was an ATP-dependent, active process. DNP-SG uptake was mediated by high- and low-affinity transport systems, and was inhibited by various Mrp inhibitors such as probenecid and indomethacin. Glutathione stimulated only the high-affinity transport system. VPA inhibited the low-affinity transport of DNP-SG, while panipenem, a CP, inhibited both high- and low-affinity transport. ATP-dependent, Mrp-mediated transport of methotrexate, another Mrp substrate, in IOVs was also observed, and VPA and various CPs inhibited the transport. The uptake of [^{3}H]VPA was examined, and found to be ATP-dependent. ATP-dependent uptake of [^{3}H]VPA was inhibited by Mrp inhibitors and panipenem, while the inhibition was not observed in the absence of ATP. These results indicate that VPA and CPs interact with Mrp-mediated transport in erythrocyte membranes, and VPA itself is transported by Mrps, which is inhibited by panipenem. Thus, the increased erythrocyte distribution of VPA by CPs observed under in vivo conditions may partly be explained by their interaction with Mrps in erythrocyte membranes.
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Keywords: Valproic acid; Carbapenem antibiotics; Drug interaction; Multidrug resistance-associated protein; Erythrocyte membrane

1. Introduction

Valproic acid (VPA) is the drug of choice for a range of generalized epilepsies. It is also used in recent years for the treatment of bipolar disorders. The ther-

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apeutic range of VPA in the plasma is fairly narrow and is considered to be about 50–100 μg/ml for the treatment of epilepsy. Therefore, therapeutic drug monitoring is recommended for the patients treated with VPA. Among various drug interactions indicated in the package insert of VPA, most serious interaction in clinical pharmacotherapy is that with carbapenem antibiotics (CPs), which leads to the drastic decrease in the serum (plasma) VPA levels and the recurrence of epileptic seizures (Nacarkucuk et al., 2004). Therefore, the concomitant use of CPs with VPA is prohibited in Japan.

So far, several mechanisms underlying the pharmacokinetic interaction between VPA and CPs have been proposed, but the mechanism is not well understood yet (Kojima et al., 1998; Yamamura et al., 2000; Torii et al., 2001; Yokogawa et al., 2001). We have recently reported that coadministration of CPs with VPA lowered plasma VPA levels and increased erythrocyte distribution of VPA in rats as well as in patients (Omoda et al., 2005). Thus, we suggested that the pharmacokinetic interaction between VPA and CPs may partly be derived from the increased erythrocyte distribution of VPA. Based on these findings, we hypothesized that, under normal condition, VPA entered into the erythrocytes is effluxed back to the plasma by efflux transporters expressing in the erythrocyte membranes, however, in the presence of CPs, the efflux of VPA is inhibited and therefore the accumulation of VPA in the erythrocytes is increased.

In rat and human erythrocyte membranes, various efflux transporters including multidrug resistance-associated protein (Mrp) 1, Mrp4, and Mrp5, as well as influx transporters including glucose transporter and monocarboxylate transporter have been detected (Mueckler et al., 1985; Garcia et al., 1994; Kartenbeck et al., 1996; Pulaski et al., 1996; Klokouzas et al., 2003). Mrps are member of ATP binding cassette (ABC) transporter family, and function as ATP-dependent efflux transporters (Ballatori et al., 2005). Among various Mrps, Mrp1 transports relatively hydrophilic compounds including glucuronide and glutathione conjugates of endogenous and exogenous compounds (Ballatori et al., 2005; Borst et al., 2000), while Mrp4 and Mrp5 transport antiviral nucleoside analogs, cAMP, and cGMP, though considerable overlapping substrate specificities are observed in these Mrps (Reid et al., 2003a).

Though there has been no information concerning VPA transport across erythrocyte membranes as far as we know, there are a small number of reports attempted to clarify the role of Mrps in VPA transport in vitro. In Caco-2 cells, transepithelial transport of VPA from the apical side to the basal side across the monolayers was shown to be enhanced by an Mrp inhibitor, pluronic P85 (Batrakova et al., 1999). Gibbs et al. (2004) examined VPA uptake in bovine brain microvessel endothelial cells (BMEC), and showed that the accumulation of VPA in the cells was increased by Mrp inhibitors such as probenecid and indomethacin, though higher concentrations of these inhibitors lowered the VPA accumulation rather than increasing it. More recently, intracellular concentration of 2′,7′-bis(2-carboxyethyl)-5(6)-carboxyfluorescein, an Mrp substrate, in BMEC was shown to be increased by the presence of VPA (Bachmeier and Miller, 2005). These results may indicate the involvement of Mrps in VPA transport in cell membranes, but are not direct evidences showing Mrp-mediated transport of VPA.

In the present study, we examined the transport characteristics of DNP-SG and methotrexate (MTX), Mrp substrates, using inside-out vesicles (IOVs) isolated from rat erythrocytes, and interaction of VPA and CPs with the transport. In addition, transport of VPA in IOVs and interaction of Mrp inhibitors and panipenem (PAPM) with VPA transport were tested. Based on these studies, the validity of the hypothesis described above was discussed.

2. Materials and methods

2.1. Materials

2-Deoxy-D-[1-^{3}H]glucose ([^{3}H]DOG) (12 Ci/mmol) was obtained from Amersham Biosciences (Buckinghamshire, UK). [4,5-^{3}H]VPA (55 Ci/mmol) was obtained from Morevek Biochemicals (Brea, CA, USA). Unlabeled VPA, MTX, probenecid, and indomethacin were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Glutathione (GSH) was from Wako Pure Chemical Industries (Osaka, Japan). Adenosine-5′-triphosphate disodium salt (ATP), creatine phosphate disodium salt, creatine phosphokinase, and taurocholic acid sodium salt (TCA) were from Nakarai Tesque (Kyoto, Japan).

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