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Drug interactions at the blood-brain barrier: Fact or fantasy?☆

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ABSTRACT

There is considerable interest in the therapeutic and adverse outcomes of drug interactions at the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB). These include altered efficacy of drugs used in the treatment of CNS disorders, such as AIDS dementia and malignant tumors, and enhanced neurotoxicity of drugs that normally penetrate poorly into the brain. BBB- and BCSFB-mediated interactions are possible because these interfaces are not only passive anatomical barriers, but are also dynamic in that they express a variety of influx and efflux transporters and drug metabolizing enzymes. Based on studies in rodents, it has been widely postulated that efflux transporters play an important role at the human BBB in terms of drug delivery. Furthermore, it is assumed that chemical inhibition of transporters or their genetic ablation in rodents is predictive of the magnitude of interaction to be expected at the human BBB. However, studies in humans challenge this well-established paradigm and claim that such drug interactions will be lesser in magnitude but yet may be clinically significant. This review focuses on current known mechanisms of drug interactions at the blood-brain and blood-CSF barriers and the potential impact of such interactions in humans. We also explore whether such drug interactions can be predicted from preclinical studies. Defining the mechanisms and the impact of drug–drug interactions at the BBB is important for improving efficacy of drugs used in the treatment of CNS disorders while minimizing their toxicity as well as minimizing neurotoxicity of non-CNS drugs.

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1. Introduction

Drug–drug interactions (DDIs) have long been recognized as an important cause of alteration in drug efficacy or adverse drug effects (or toxicity), particularly for drugs that have a narrow therapeutic window. Much of the work on DDIs has been focused on changes in absorption, bioavailability or systemic concentration of the drug (Levy et al., 2000). However, it has been increasingly recognized that DDIs can affect the distribution of drugs into a particular compartment (e.g. CNS) with or without affecting their systemic plasma (or blood) concentration. Furthermore, DDIs can result in CNS effects of medications that normally are not targeted to the brain (Endres et al., 2006).

DDIs that involve the CNS can result from 1) changes in plasma concentrations (unbound or total) of at least one of the interacting drugs (pharmacokinetic interactions), 2) changes in drug's effects at target sites or its disposition within the CNS (pharmacodynamic and pharmacokinetic interactions, respectively), or a combination of the two (Table 1). A third source for altered effects of drugs on the CNS resides in the interfaces between plasma and the CNS, namely the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier

Abbreviations: ABC, adenosine triphosphate binding cassette; AUC, area under the concentration-time curve; BBB, blood-brain barrier; BBBD, blood-brain barrier disruption; BCRP, breast cancer resistance protein; BCSFB, blood cerebrospinal fluid barrier; CNT, concentrative nucleoside transporter; CP, choroid plexus; CSF, cerebrospinal fluid; DDI, drug-drug interaction; ENT, equilibrative nucleoside transporter; GST, glutathione S-transferase; ISF, interstitial fluid; KO, knockout; MCT, monocarboxylate transporter; MDR, multidrug resistance; MRP, multidrug resistance-associated protein; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, OCTN, organic cation transporter; PET, positron emission tomography; P-gp, P-glycoprotein; PXR, pregnane X receptor; SLC, solute carrier; TJs, tight junctions; WT, wild type.

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Table 1
Examples of different types of drug interactions that affect CNS drug concentrations and activity in humans.

Type of interaction	Classification	Example	Putative mechanism of interaction	Outcome	Reference
Altered transfer of object drug across the BBB	Pharmacokinetic	Verapamil-cyclosporine	Inhibition of P-glycoprotein-mediated efflux of verapamil from brain to plasma	Increased brain concentrations of verapamil	Sasongko et al., 2005
Altered plasma concentrations of object drug	Pharmacokinetic	Phenytoin-carmustine, vinblastin, methotrexate	Enhanced systemic metabolism of phenytoin by vinca alkaloids	Decreased plasma concentrations of phenytoin, recurrent seizures	Bollini et al., 1983; Vecht et al., 2003
Altered pharmacokinetics of object drug within the CNS	Pharmacokinetic	Levodopa-tolcapone	Inhibition of levodopa metabolism in brain parencyma[a]	Improved efficacy of levodopa	Ceravolo et al., 2002; Deleu et al., 2002
Altered binding of object drug to target site(s) in the CNS	Pharmacodynamic	Benzodiazepines-flumazenil	Inhibition of benzodiazepine binding to GABAergic receptors	Reversal of benzodiazepine overdose	Betten et al., 2006; Shinotoh et al., 1989

[a] Tolcapone inhibits peripheral metabolism of levodopa as well.

(BCSFB). By modulating BBB or BCSFB function, a drug can affect the distribution of another drug into the brain, its removal from the brain, or both. In this case, the plasma concentration of the affected drug often remains unchanged, especially when only a small fraction of the dose distributes into the brain. To distinguish between barrier-mediated interactions and those caused by other mechanisms, the concentration of the affected drug should be measured in the CNS, in the presence and the absence of the precipitant drug. In the clinical setting, however, brain concentrations are normally not measured due to technical and ethical reasons. Thus, BBB-based interactions may be overlooked or confused with pharmacodynamic interactions. From the clinical point of view, DDIs that seem to be unexpected could potentially be prevented if their mechanisms are correctly identified.

The aim of this review is to present an overview of currently known mechanisms of drug interactions at blood–brain interfaces and the potential impact of such interactions on CNS drug disposition and effects. Particularly, we will focus on transporter-mediated DDIs. Most of the existing knowledge on DDIs at the BBB is based on studies in animal models, but few clinical studies and case reports are also available. In vitro studies are beyond the scope of this review, but general principles for prediction of DDIs at the human BBB from in vitro studies as well as from studies in animal models are presented. Detailed discussion of BBB structure and function and methodologies for evaluation of brain penetration of drugs are available elsewhere (Langer & Müller, 2004; Redzic & Segal, 2004; Shen et al., 2004; Hawkins & Davis, 2005; Endres et al., 2006;

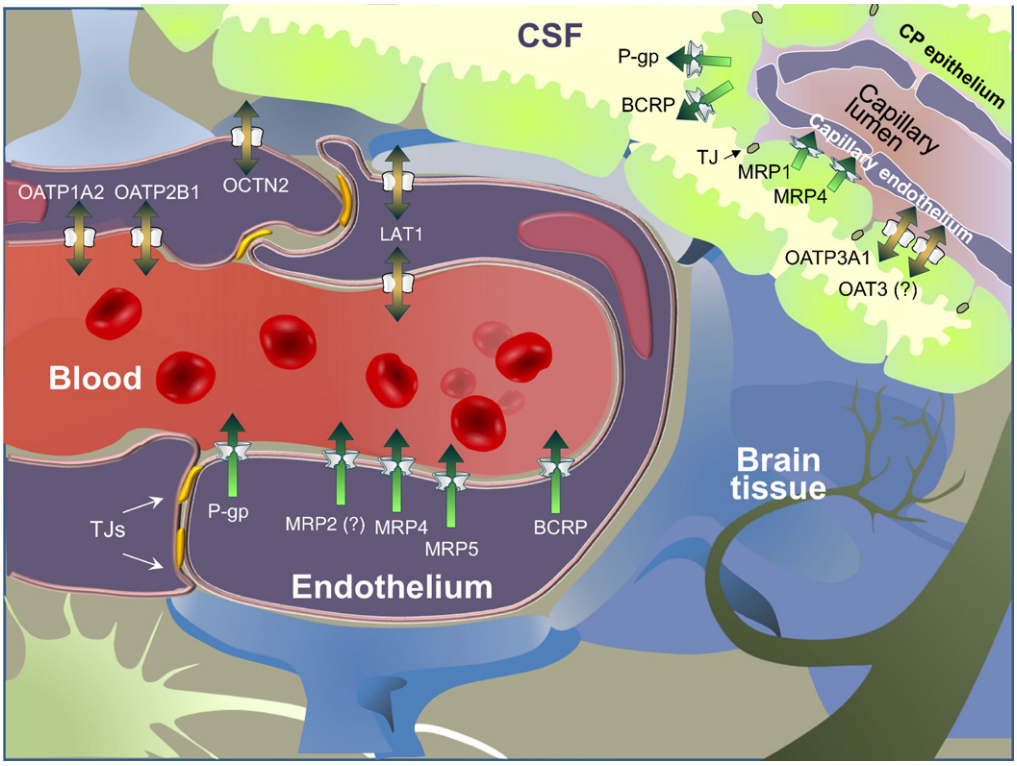

Fig. 1. The localization of transporters at blood-brain barriers. The blood-brain barrier (BBB) is formed by capillary endothelial cells, sealed together by tight junctions. The blood-cerebrospinal fluid barrier (BCSFB) is formed by epithelial cells of the choroid plexus, and tight junctions limit drug transfer between blood and CSF. Under normal conditions, these two anatomical barriers make the brain almost inaccessible to polar drugs, unless they are transferred into the CNS by influx transport systems. Some of these transporters can transfer drugs bidirectionally, down their concentration gradients. Efflux transporters at the luminal membranes of the BBB and the BCSFB remove drugs from brain interstitial fluid back to blood or into the CSF, respectively, thereby preventing them from producing CNS effects. The role of efflux transporters located on the abluminal membranes is unclear. In addition, several drug metabolizing enzymes can potentially form an enzymatic barrier to drug distribution into the brain. BCRP, breast cancer resistance protein; CP, choroid plexus; LAT, L-amino acid transporter; MRP, multidrug resistance-associated protein; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCTN, organic cation/carnitine transporter; P-gp, P-glycoprotein.