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Efflux transport systems at the blood–brain barrier and blood CSF barrier

Hiroyuki Kusuhara, Yuichi Sugiyama*

Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Abstract. Drugs acting in the central nervous system (CNS) have to cross the blood-brain barrier (BBB) and/or blood–cerebrospinal fluid barrier (BCSFB). These two barriers are formed by brain capillary endothelial cells and choroid plexus epithelial cells. P-glycoprotein (P-gp) was initially identified as an efflux transporter at the BBB. It extrudes its substrate drugs into the blood, and acts as one of barrier functions against invasion of xenobiotics into the central nervous system. Thus, recognition by P-gp as a substrate is a major disadvantage for drugs used to treat CNS disease. In addition to P-gp, accumulating evidence has revealed the presence of efflux transport systems for anionic drugs. The transporters involved in the efflux transport of organic anions from the CNS are being identified in the BBB and BCSFB, and include the members of organic anion transporting polypeptides (Oatp1a4 and Oatp1a5) and organic anion transporter (Oat3) which are involved in the efflux of amphipathic and hydrophilic organic anions, respectively. The transporters located on the membranes facing the blood still remain to be identified although several candidate primary active transporters, such as MRP and BCRP, have already been proposed. Further clarification of influx and efflux transporters in the barriers will enable us to deliver drugs efficiently into the brain and to understand the mechanisms of drug–drug interactions and interindividual differences in the therapeutic CNS effects and/or adverse effects caused by drugs. The present manuscript summarizes the recent advance in the characterization of efflux transport systems at the BBB and BCSFB from our laboratory and others.

Keywords: Efflux transport; Organic anion; OATP; OAT; MRP; BCRP

* Corresponding author. Tel.: +81 3 5841 4770; fax: +81 3 5841 4766.
E-mail address: sugiyama@mol.f.u-tokyo.ac.jp (Y. Sugiyama).

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1. Introduction

Brain capillary endothelial cells (BCEC) are characterized by the paucity of fenestra and pinocytotic vesicles and the highly developed tight junctions between adjacent endothelial cells [1]. These anatomical properties allow the BCEC to act as a static wall between the brain and circulating blood, and thus, the brain capillaries are referred to as the blood–brain barrier (BBB). The blood–cerebrospinal fluid barrier (BCSFB) is another barrier between the cerebrospinal fluid (CSF) and blood formed by a tight monolayer of choroid plexus epithelial cells [2]. In addition, it is well accepted that active efflux mechanisms at the BBB restrict the brain penetration of xenobiotics. Drugs have to overcome such efflux mechanisms to achieve clinically significant concentrations in the central nervous system.

P-glycoprotein (P-gp) is a well-known transporter acting as a gate-keeper protein for xenobiotics at the BBB [3,4]. P-gp is a primary active transporter, and extrudes a variety of hydrophobic neutral and cationic compounds, and certain kinds of organic anions to the blood side. Apart from lipophilic compounds, transporters are involved both in uptake and efflux to enable efficient vectorial transport across the endo- and epithelial cells. The members of the SLCO/SLC21 and SLC22 family play an important role in the elimination of xenobiotics from the liver and kidney, respectively. Cumulative studies have demonstrated that these members also play important roles in the efflux transport of

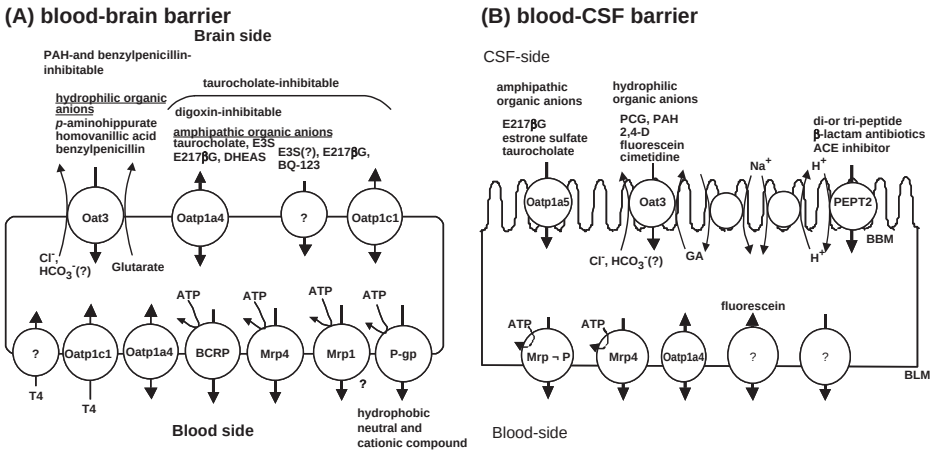

Fig. 1. Schematic diagram of the efflux transport mechanisms at the BBB and BCSFB. (A) The efflux mechanism for hydrophilic organic anions is accounted for by Oat3, and that for amphipathic organic anions is accounted for partly by Oatp1a4 (taurocholate- and digoxin-inhibitable pathway) and partly by an, as yet, unknown transporter. It has been suggested that the unknown transporter is involved in the efflux of E3S, E217βG and BQ-123. On the luminal membrane, Oatp1a4 and Oatp1c1 are involved in the uptake of amphipathic organic anions and peptides, and T4. ABC transporters, such as MRP1, MRP4 and BCRP, have been identified as candidate. (B) The uptake of hydrophilic organic anions is accounted for by Oat3, and that of amphipathic organic anions is accounted for by Oatp1a5. A peptide transporter (PEPT2) has been identified as an uptake mechanism for di- or tripeptide and peptide mimetic drugs. On the basolateral membrane, Oatp1a4 and Oatp1c1 are involved in the uptake of amphipathic organic anions and peptides, and T4. ABC transporters, such as MRP1 and MRP4, have been identified as being involved in the efflux of organic anions.