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Role of drug efflux transporters in the brain for drug disposition and treatment of brain diseases

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Abstract

The blood–brain barrier (BBB) serves as a protective mechanism for the brain by preventing entry of potentially harmful substances from free access to the central nervous system (CNS). Tight junctions present between the brain microvessel endothelial cells form a diffusion barrier, which selectively excludes most blood-borne substances from entering the brain. Astrocytic end-feet tightly ensheath the vessel wall and appear to be critical for the induction and maintenance of the barrier properties of the brain capillary endothelial cells. Because of these properties, the BBB only allows entry of lipophilic compounds with low molecular weights by passive diffusion. However, many lipophilic drugs show negligible brain uptake. They are substrates for drug efflux transporters such as P-glycoprotein (Pgp), multidrug resistance proteins (MRPs) or organic anion transporting polypeptides (OATPs) that are expressed at brain capillary endothelial cells and/or astrocytic end-feet and are key elements of the molecular machinery that confers the special permeability properties to the BBB. The combined action of these carrier systems results in rapid efflux of xenobiotics from the CNS. The objective of this review is to summarize transporter characteristics (cellular localization, specificity, regulation, and potential inhibition) for drug efflux transport systems identified in the BBB and blood–cerebrospinal fluid (CSF) barrier. A variety of experimental approaches available to ascertain or predict the impact of efflux transport on brain access of therapeutic drugs also are described and critically discussed. The potential impact of efflux transport on the pharmacodynamics of agents acting in the CNS is illustrated. Furthermore, the current knowledge about drug efflux transporters as a major determinant of multidrug resistance of brain diseases such as epilepsy is reviewed. Finally, we summarize strategies for modulating or by-passing drug efflux transporters at the BBB as novel therapeutic approaches to drug-resistant brain diseases.

Contents

Abbreviations: ABC, ATP-binding cassette; AIDS, immunodeficiency syndrome; BBB, blood–brain barrier; BCRP, breast cancer related protein; CNS, central nervous system; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; HPA axis, hypothalamic–pituitary–adrenal axis; MDR, multidrug resistance; MRP, multidrug resistance protein (or multidrug resistance-associated protein); MVP, major vault protein; OAT, organic anion transporter; OATP, organic anion transporting-polypeptide; PET, positron emission tomography; Pgp, P-glycoprotein; RT-PCR, reverse transcription-polymerase chain reaction; SPECT, single photon emission computed tomography

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1. Introduction

Transportation of molecules across the cell membrane in living organisms is a critical aspect of life. Transportation includes importation of nutrients from the environment and exportation of toxic compounds. When export includes therapeutic compounds, then the practice of clinical medicine may become compromised. The importance of drug efflux transporters in disease processes and treatment has become increasingly evident in recent years (Borst and Elferink, 2002; Chang, 2003; Lage, 2003; Leonard et al., 2003; Schinkel and Jonker, 2003; Sakaeda et al., 2004). With the sequencing of the human genome, it has been estimated that approximately 500–1200 genes code for drug transporters (Sakaeda et al., 2004). Drug efflux transporters have a major impact on the pharmacological behavior of most clinically used drugs, critically affecting drug absorption, disposition, and elimination in the body (Fromm, 2000; Ayrton and Morgan, 2001; Borst and Elferink, 2002; Schinkel and Jonker, 2003; Fromm, 2004). Furthermore, such transporters are involved in the emergence of "multidrug resistance" (MDR), which plays a crucial role in the failure of treatments of tumors, infectious diseases and several brain disorders (Ling, 1997; Lage, 2003). Among the mechanisms underlying the multidrug resistance phenomenon in various organisms is the action of transmembrane transport proteins that catalyse the active expulsion of functionally unrelated drugs out of the cell or their intracellular partitioning (Lage, 2003). Often this efflux of therapeutic compounds is mediated by a large superfamily of proteins referred to as multidrug resistance proteins, most of which belong to the family of ATP-binding cassette (ABC) transporters. ABC transporters are multidomain integral membrane proteins that utilise the energy of ATP hydrolysis to translocate solutes across cellular membranes in all mammalian species (Jones and George, 2004). ABC transporters form one of the largest of all protein families and are central to many important biomedical phenomena, including resistance of cancers and pathogenic microbes to drugs (Borges-Walmsley et al., 2003). Elucidation of the structure and function of ABC transporters is essential to the rational design of agents to control their function.