Review

Functional Expression and Localization of P-glycoprotein in the Central Nervous System: Relevance to the Pathogenesis and Treatment of Neurological Disorders

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Received February 9, 2004; accepted April 16, 2004

The expression of membrane drug transport systems in the central nervous system plays an important role in the brain disposition and efficacy of many pharmacological agents used in the treatment of neurological disorders such as neoplasia, epilepsy, and HIV-associated dementia. Of particular interest is P-glycoprotein, a membrane-associated, energy-dependent, efflux transporter that confers the multidrug resistance phenotype to many cells by extruding a broad range of xenobiotics from the cell, resulting in poor clinical outcomes. In addition, the expression pattern of P-glycoprotein has recently been suggested to play a key role in the etiology and pathogenesis of certain diseases such as Alzheimer’s and Parkinson’s diseases. This review will focus on the cellular localization, molecular expression, and functional activity of P-glycoprotein in several compartments of the central nervous system and address its relevance in the pathogenesis and pharmacological treatment of neurological disorders.

KEY WORDS: brain; neurological diseases; P-glycoprotein; transporter.

INTRODUCTION

Membrane drug transporters and their modulatory effects on drug therapy is an area of research that is growing in interest and momentum, particularly in the field of neuropharmacology. P-glycoprotein (P-gp), an efflux drug transporter, has received particular attention during the years after this protein was discovered to play a key role in the multidrug resistance (MDR) phenotype of some cancer cells. In addition to being expressed in cancer cells, P-gp has been localized to many normal tissues of the body such as the intestine, kidney, blood-brain barrier (BBB), blood-cerebrospinal fluid (BCSF) barrier, blood-testis barrier, pancreas, and in peripheral immune cells. Although no definite physiological role has yet been determined for P-gp, the polarized expression of this protein at various barriers suggests that it may serve to protect the cells from the accumulation of toxic xenobiotics. In vivo and in vitro studies suggest that the efflux of many pharmacological agents out of cells is mediated by P-gp. More specifically, studies show P-gp to be expressed and functionally active in specific areas of the brain such as the BBB, BCSF barrier, astrocytes, and microglia. In the clinical setting, some brain pathologies (brain neoplasia, epilepsy, HIV-associated dementia) that have shown either poor initial response or acquired resistance to drug therapy express up-regulated levels of P-gp along their cell plasma membranes.

With the discovery of the role of P-gp in drug resistance and disease pathology, much effort has been invested into developing compounds that inhibit P-gp function as adjuncts to therapy. Unfortunately, the clinical efficacy of the first and second-generation P-gp inhibitors has proven to be quite disappointing to say the least, primarily due to their high toxicity profiles (1–3). In addition, the expression of several other families of membrane drug transporters with overlapping substrate specificities poses a significant problem. The more recently developed third generation of P-gp inhibitors show greater specificity and lower toxicity profiles than their predecessors. Their safety and efficacy, however, remains to be demonstrated in clinical trials (4–7). It is believed that these inhibitors may be valuable agents in circumventing the current problems associated with drug resistance in the treatment of brain neoplasias, epilepsy, and HIV-associated dementia. In the case of Alzheimer’s and Parkinson’s diseases, it seems as though the expression levels of P-gp may be involved in the etiology and pathogenesis of these conditions.

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ABBREVIATIONS: AD, Alzheimer’s disease; AEDs, antiepileptic drugs; BBB, blood-brain barrier; BCSF, blood-cerebrospinal fluid; BCRP, breast cancer resistance protein; BMRP, brain multidrug resistance protein; CNS, central nervous system; CP, choroid plexus; CR-3, complement 3 receptor; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; HAART, highly active antiretroviral therapy; HAD, HIV-associated dementia; HIV, human immunodeficiency virus; MDR, multidrug resistance; MRP, multidrug resistance protein; PBMC, peripheral blood mononuclear cell; PD, Parkinson’s disease; P-gp, P-glycoprotein; PI, protease inhibitor; RT-PCR, reverse transcriptase polymerase chain reaction.
FUNCTIONAL AND MORPHOLOGICAL CHARACTERISTICS OF THE BRAIN VASCULAR BARRIERS AND BRAIN PARENCHYMA

Brain Vascular Barriers (Blood-Brain Barrier, Blood-Cerebrospinal Fluid Barrier)

The CNS is a delicate microenvironment containing about $10^{11}$ neurons and at least 1000-fold more dendrites where various interactions and electrical impulses are produced every second. These multifaceted interactions result in reactions ranging from autonomic responses to voluntary movements to higher cognitive functions of memory and thought (8). Two physiological barriers that separate it from the rest of the body, the BBB and the BCSF barrier, keep this highly complex environment under strict homeostatic control.

The BBB is composed of brain endothelial cells that line the cerebral vasculature (Fig. 1a). Tight junctions seal these cerebral endothelial cells together to prevent the bulk flow of water and solutes (9) (Fig. 1b). In fact, brain capillaries are about 50–100 times tighter than peripheral microvessels (10). Furthermore, the physical barrier properties of the BBB also include the absence of intercellular clefts, lack of fenestrations, minor pinocytic activity, and a high transendothelial electrical resistance of about 1500–2000 Ohm cm\(^2\) (11,12).

The outer surface of the endothelium is surrounded by the end feet of neighboring astrocytes and pericytes (13). In addition to the physical barrier properties, the cerebral endothelial cells display an asymmetric array of receptors, ion channels, and transporters that function in a dynamic manner to regulate the influx and efflux of molecules, some of which are biologically important and others potentially toxic to the brain.

There are many pathways of drug transport across the various cell membranes of the brain (14,15) (Table I). The mechanism of transport will depend on the physicochemical characteristics of the drug as well as the barrier properties of the brain microvasculature and choroid plexus. One transport pathway is passive permeability of water-soluble drugs across aqueous channels. This method of transport largely depends on the molecular size of the drug. Generally, transport and permeability of compounds with a molecular weight larger than 150–200 is restricted from crossing due to the small openings of aqueous channels of the cell membrane. Examples of highly water-soluble drugs that cross by simple passive diffusion via aqueous channels are acetylsalicylic acid, nicotine, caffeine, and vitamin C (14). Some lipid-soluble drugs cross cell membranes by passive transport between the lipid molecules of the cell membrane. This is largely determined by the following physicochemical characteristics of the drug itself: concentration or dose, oil/water partition coefficient, concentration of proton, and surface area for drug diffusion (14,15). Specialized vesicles that are highly expressed along the cerebral endothelial cell (16) carry out general endocytotic and transcytotic processes. Caveolae are specialized microdomains of the endothelial cell plasmalemma that are rich in cholesterol and exhibit various surface markers such as caveolins, Ca\(^{2+}\)-ATPase, alkaline phosphatase, and 5'-nucleotidase that distinguish it from the plasmalemmal portion of the cells (16,17). Functionally, caveolae have been implicated in various transport mechanisms across the BBB such as transcytosis (16), potocytosis (18), and endocytosis (include pinocytosis and phagocytosis) (19,20) of various substances including plasma proteins, drugs, immunoglobulins, and metalloproteins (16). Caveolae are also involved in major processes such as signal transduction (21). The endocytosis of molecules is accomplished through nonspecific (via fluid phase endocytosis or adsorptive mechanisms) or specific receptor-mediated pathways. Once ingested, these substances may undergo transcellular transfer between cellular compartments either by fluid phase, adsorptive, or receptor-mediated mechanisms via caveolae (16). In addition, molecules cross the barriers by facilitated diffusion processes via specific carriers (i.e., GLUT-1, A and L-system amino acid transporters) (22) (Fig 2). These essential nutrients and drugs that use facilita-