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Cerebral expression of drug transporters in epilepsy ☆

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ABSTRACT

Over-expression of drug efflux transporters at the level of the blood–brain barrier (BBB) has been proposed as a mechanism responsible for multidrug resistance. Drug transporters in epileptogenic tissue are not only expressed in endothelial cells at the BBB, but also in other brain parenchymal cells, such as astrocytes, microglia and neurons, suggesting a complex cell type-specific regulation under pathological conditions associated with epilepsy. This review focuses on the cerebral expression patterns of several classes of well-known membrane drug transporters such as P-glycoprotein (Pgp), and multidrug resistance-associated proteins (MRPs) in the epileptogenic brain. Both experimental and clinical evidence of epilepsy-associated cerebral drug transporter regulation and the possible mechanisms underlying drug transporter regulation are discussed. Knowledge of the cerebral expression patterns of drug transporters in normal and epileptogenic brain will provide relevant information to guide strategies attempting to overcome drug resistance by targeting specific transporters.

Contents

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1. Expression and function of drug transporters in the normal brain

Drug transporters represent well recognized active carrier systems that play key roles in the absorption, distribution and secretion of therapeutic agents. Knowledge of the extent of the transporter family has grown rapidly during the last years and considerable progress has been made in understanding their function and expression in different tissues and cell types. Many transporters that have been first characterized in peripheral tissues, have now also been detected in the brain and have been shown to be involved in the influx and efflux of a variety of endogenous or exogenous substances [1,2]. Thus, drug transport at the blood–brain barrier (BBB), as well as at the level of the blood–cerebrospinal barrier, is a result of a complex and concerted action of different efflux and influx pumps (transporters). Most drug transporters are members of one of two major superfamilies: the solute-linked carrier (SLC) superfamily and the adenosine triphosphate (ATP)-binding cassette (ABC) transporter superfamily [3].

1.1. Organic cation and anion transporters

The (SLC) superfamily includes organic cation and anion transporters (OCT/OAT) [4]. The organic cation transport (OCT) system including two subtypes (H^+ gradient-dependent transporters, OCTN1 and OCTN2; and potential-sensitive transporters, OCT1, OCT2, OCT3), has been extensively characterized in the intestine, liver and kidney [1,5,6]. The OCTs recognize a variety of endogenous and exogenous organic cations as substrates, including cationic neurotoxins and monoamine neurotransmitters, which are substrates of OCT1, OCT2 and OCT3. There is evidence for the expression of OCTs in the brain (for review see [2,6]). OCT2 is expressed in neurons; expression of both OCT1 and OCT2 has been detected in brain microvessel endothelial cells [7] and OCTN2 and OCT3 are expressed in several different brain regions, including cerebellum, hippocampus and cerebral cortex [6,8,9].

The organic anion transport system includes several families of organic anion transporters, such as the organic anion transporter polypeptide (OATP), and the organic anion transporter (OAT) families. Several members of these families have been detected in the brain, such as OATP1 and OATP2 and OAT3, which have been suggested to play a role in the detoxification of endogenous anionic substrates from the brain (for reviews see [1,2]).

Future studies focusing on the cerebral localization and regulation of these carriers are essential to elucidate more precisely their physiological role in the CNS. Recently, OATP2 and P-glycoprotein (Pgp; member of the ATP-binding cassette transporter superfamily), have been shown to colocalize in rat brain capillary endothelium and choroid plexus epithelium [10]. However, whether these transporters could work together to regulate the penetration of drugs into the brain remains to be elucidated.

1.2. Efflux transport systems (ATP-binding cassette, ABC transporters)

ABC transporters represent a large family of transmembrane proteins that utilize the energy of adenosine triphosphate (ATP) hydrolysis to transport a wide range of substrates across cellular membranes [11–13]. They fulfill a large number of biological functions and are expressed in many biological interfaces such as the intestine, liver, kidney, and also at the level of the BBB [13,14].

Increasing evidence supports the role of ABC transporters in various drug-resistant brain disorders [13] and attention has been particularly focused on transporters, such as P-glycoprotein (Pgp; ABCB1), members of the subfamily of multidrug resistance-associated proteins (MRPs; according to new nomenclature ABCC transporter family) and breast-cancer resistance protein (BCRP; ABCG2).

1.2.1. P-glycoprotein (Pgp)

Pgp, a product of the *ABCB1* (known as multidrug resistance 1; MDR1) gene, is a transmembrane glycoprotein, with a molecular weight of about 170 kDa. It has been discovered in the 1970s in Chinese hamster ovary cells selected for resistance to colchicine [15], as a membrane efflux pump involved in the phenomenon of multidrug resistance (MDR) in tumor cells [16]. Pgp is widely expressed in tissues with excretory functions, including kidney, liver, pancreas, small and large intestine [17–19], as well as in blood mononuclear cells [20]. Pgp has been detected in endothelium of both arterioles and capillaries of heart samples [21], and Pgp expression in cardiomyocytes has been observed under hypoxic conditions [22].

In addition, Pgp has been demonstrated to represent a key element of the blood–brain barrier (BBB), being actively involved in the transport of a variety of lipophilic drugs out of the brain capillary endothelial cells [13]. Although contradictory observations have been obtained by testing the interaction between anti-epileptic drugs (AEDs) and Pgp, recent in vitro data indicate that common AEDs are also substrates of human Pgp ([23]; see also review addressing this topic within this issue).

1.2.2. Pgp expression in the brain

Numerous immunocytochemical studies in both rodent and human have confirmed the expression of Pgp at the cellular level in the capillary endothelial cells of the BBB in normal brain and in epithelial cells of the choroid plexus [24–33]. Several studies have demonstrated that Pgp is expressed early during human cerebral cortical microvessel development [34–37]. Pgp is expressed at the luminal side of the endothelial cells and in the caveolae, which are membrane invaginations involved in transport of macromolecules across cells by transcytosis [38]. Localization of Pgp in astrocyte endfeet processes at the abluminal face of human brain microvasculature has been reported using unfixed isolated human brain capillaries [39]. Schlachetzki and Pardridge demonstrated that Pgp is expressed in both astrocytic endfeet and microvascular endothelium in healthy rhesus monkey brain using fresh-frozen brain tissue [40]. These apparently conflicting results suggest that detection of Pgp by immunohistochemistry is highly sensitive to tissue fixation and staining conditions [41]. Using different staining techniques, there is now substantial evidence that Pgp is not limited to the BBB, but can also involve other parenchymal cells in the CNS such as astrocytes, microglia and neurons, in particular during pathological conditions [42–44]. More recently, it has been suggested that Pgp expression might be induced in a subclass of astrocytes in the developing brain [36].

Moreover, it has been suggested that neuronal Pgp expression has a protective function by preventing exposure to toxic levels of compounds that might further damage the cells [45]. Apart from removal of xenobiotics, Pgp can also regulate cell survival by a drug efflux-independent mechanism via extrusion of cytokines and modulation of intracellular of pH [46]. Recent data support a role of Pgp as a key modulator of adaptive immunity, modulating the secretion of inflammatory molecules [47,48].

At the subcellular level, Pgp is also localized in intracellular vesicles where drugs are sequestered away from their subcellular targets [49,50].

1.2.3. Multidrug resistance-associated proteins (MRPs)

Members of the MRP subfamily have been also associated with MDR in various brain disorders [13,51,52]. However, some controversy exists about the expression of the different MRP isoforms at the level of the BBB [13,51,53]. Variable levels of expression of MRP1-6 have been reported in human brain capillary endothelial cells [27,54]. A recent study [55] confirms presence of mRNAs of different MRPs (including MRP1, MRP4 and MRP5) in isolated brain microvessel endothelial capillaries. However, species differences exist in the expression of a number of transporters. Using immunocytochemistry,