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Regulation of ABC Efflux Transporters at Blood-Brain Barrier in Health and Neurological Disorders

Hisham Qosa[a,*], **David S. Miller**[b], **Piera Pasinelli**[a], and **Davide Trotti**[a,*]

[a] Weinberg Unit for ALS Research, Farber Institute for Neuroscience, Department of Neuroscience, Thomas Jefferson University, 900 Walnut street, Philadelphia, PA 19107, USA

[b] Laboratory of Signal Transduction, NIH/NIEHS, Research Triangle Park, NC 27709, USA

Abstract

The strength of the blood-brain barrier (BBB) in providing protection to the central nervous system from exposure to circulating chemicals is maintained by tight junctions between endothelial cells and by a broad range of transporter proteins that regulate exchange between CNS and blood. The most important transporters that restrict the permeability of large number of toxins as well as therapeutic agents are the ABC transporters. Among them, P-gp, BCRP, MRP1 and MRP2 are the utmost studied. These efflux transporters are neuroprotective, limiting the brain entry of neurotoxins; however, they could also restrict the entry of many therapeutics and contribute to CNS pharmacoresistance. Characterization of several regulatory pathways that govern expression and activity of ABC efflux transporters in the endothelium of brain capillaries have led to an emerging consensus that these processes are complex and contain several cellular and molecular elements. Alterations in ABC efflux transporters expression and/or activity occur in several neurological diseases. Here, we review the signaling pathways that regulate expression and transport activity of P-gp, BCRP, MRP1 and MRP2 as well as how their expression/activity changes in neurological diseases.

Keywords

ABC efflux transporters; blood-brain barrier; neuroprotection; pharmacoresistance

Introduction

Since its discovery by Paul Ehrlich in 1885 and for more than 100 years of extensive research, blood-brain barrier (BBB) has been recognized as a dynamic and highly organized interface between brain and blood that prevents free passage of solutes and protects the CNS by isolating it from the periphery (Ribatti et al., 2006). The discovery of ABC efflux

* Corresponding author: hisham.qosa@jefferson.edu (H. Qosa), davide.trotti@jefferson.edu (D. Trotti).

Conflict of interest

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transporters in the early 1970s and subsequent demonstration of their expression within the BBB added an important element that contributes barrier function. ABC efflux transporters are a challenging research field because of their complex regulation at the BBB, both in physiological and pathological conditions. Moreover, the overlap in substrate recognition and function of these transporters adds an additional level of complexity to the understanding of their role and regulation (Miller, 2010). Here, we present an overview of the pathways that regulate the major ABC efflux transporters at BBB and their dysregulation in neurological disease.

The blood-brain barrier

The blood-brain barrier (BBB) is a selectively restrictive interface between the vascular system and the CNS that maintains brain homeostasis by regulating the chemical environment, immune cell transport, and the entry and disposition of xenobiotics (Hawkins and Davis, 2005). The layer of endothelial cells (ECs) that form the vessel/capillary walls defines the BBB (Ballabh et al., 2004). More recently, the concept of the neurovascular unit has been introduced to recognize the functional interactions among neurons and non-neuronal cells, such as vascular cells (ECs and pericytes) and glia (astrocytes, microglia, and oligodendroglia), in regulating the function of BBB (Abbott et al., 2010; Abbott, 2013; Hawkins and Davis, 2005). However, the EC layer lining the brain capillaries is the main infrastructure of the BBB that forms the physical barrier against free movement of drugs, xenobiotics, endogenous peptides and other circulating compounds (Abbott et al., 2006; Wong et al., 2013). In addition to the BBB, capillaries in the spinal cord form a blood-spinal cord barrier (BSCB) that is similar in structure and function to the brain ECs (Campos et al., 2012; Wang et al., 2014). Within CNS barriers, ECs are polarized cells with an apical membrane facing the blood (luminal membrane) and a basolateral membrane facing the brain tissue (abluminal membrane) and anchored to a continuous basement membrane; ECs are connected to each other by tight and adherens junctions (Wong et al., 2013). Tight junctions (TJ) between adjacent ECs contain transmembrane TJ proteins, occludin, claudins and junctional adhesion molecules (JAMs), and adaptor molecules that connect TJ proteins to the actin cytoskeleton. Similarly, adherens junctions (AJ) consist of transmembrane AJ proteins VE-cadherin and catenin, and adaptor molecules that link AJ proteins to the actin cytoskeleton (Abbott et al., 2010; Zlokovic, 2008). Although a sealed EC monolayer forms a restrictive barrier that precludes free movement of substances between blood and brain, these cells express a wide range of transport proteins and receptors that modulate the movement of solutes across the BBB (Cecchelli et al., 2007). It has been estimated that these transporters constitute 10–15% of all proteins in the neurovascular unit (Enerson and Drewes, 2006). Four types of transport protein are expressed at the BBB; ion channels, solute transporters, aquaporins, and ATP-powered pumps. ATP-powered pumps or ABC transporters play critical roles in neuroprotection and pharmacoresistance (Vasiliou et al., 2009).

ABC transporters at BBB

ATP-binding cassette (ABC) transporters comprise one of the largest protein superfamilies, with members found in all living organisms, from microbes to humans. In humans, 49 genes encode for ABC transporters; these are classified into seven subfamilies, designated A to G,

on the basis of sequence homology and functional similarities (Moitra and Dean, 2011; Vasiliou et al., 2009). ABC transporters are ubiquitous membrane-bound proteins that utilize ATP hydrolysis to drive the transport of a vast array of lipophilic, amphipathic substrates across membranes (Loscher and Potschka, 2005b). ABC transporters are critically important in several physiological functions and defects in many of these transporters are associated with severe inherited disorders (Moitra and Dean, 2011). ABC transporters are expressed in most cells, but they are most highly expressed in barriers (blood-brain barrier, blood-spinal cord barrier, blood-cerebrospinal fluid barrier, blood-testis barrier, and blood-placental barrier) (Aye and Keelan, 2013; Campos et al., 2012; Hartz and Bauer, 2011; Leslie et al., 2005; Robillard et al., 2012), excretory tissues (liver and kidney) (Choi and Yu, 2014) and absorption tissues (intestine and colon) (Oude Elferink and de Waart, 2007). In human BBB, three ABC subfamilies, B, C, and G, contain efflux transporters that extrude metabolic waste products, foreign chemicals (xenobiotics), and a large number of drugs from the brain into the blood (Hartz and Bauer, 2011). Among these subfamilies, ABCB1 (multidrug resistance proteins; MDR1 or P-gp), ABCC (multidrug resistance-associated protein; MRPs), and ABCG2 (breast cancer resistance protein; BCRP) are the best-studied (Hartz and Bauer, 2011; Miller, 2015). We will focus our discussion on the mechanisms that regulate expression and activity of these three transporters in the endothelium of BBB, their dysregulation in neurological disease, and their contribution to neuroprotection and development of CNS pharmacoresistance.

ABCB1—ABCB1 or P-glycoprotein (P-gp) is the 170-kDa glycoprotein product of the MDR1 gene that is highly expressed on the luminal membrane of the endothelial cells at the BBB, and to a much lesser extent in brain parenchyma, neuronal, and glial cells (Loscher and Potschka, 2005b; Sharom, 2008). Several studies have reported that astrocyte and microglial cultures express low levels of P-gp (Decleves et al., 2000; Ronaldson et al., 2004), while other studies did not confirm these findings (Daood et al., 2008; Volk et al., 2005). These contradictions suggested that P-gp expression in brain parenchymal cells is nominal, although it may be significantly enhanced in pathologic conditions, for example, amyotrophic lateral sclerosis (ALS) (Jablonski et al., 2012), epileptic seizures (Bauer et al., 2008), focal cortical dysplasia (Ak et al., 2007), and brain tumors (Aronica et al., 2003; Haar et al., 2012; Lin et al., 2014).

P-gp is composed of two homologous and highly conserved six-transmembrane proteins interconnected by a central cytoplasmic linker domain with a large substrate-binding pocket within the plasma membrane (Aller et al., 2009; Hennessy and Spiers, 2007). In addition, P-gp is subjected to post-translational modifications, in particular glycosylation in the Golgi apparatus, to form the mature core glycosylated protein. Previous studies suggested that glycosylation protects P-gp from degradation and mislocalization (Fu and Arias, 2012; Perego et al., 2010). Strategic localization of P-gp at the luminal membrane of BBB endothelial cells and its wide substrate selectivity make it an effective defense against a wide spectrum of endogenous ligands, therapeutic drugs and xenobiotics (Miller et al., 2008). Therefore, P-gp is widely believed to be the most important ABC transporter in the CNS that plays a crucial role in both neuroprotection and pharmacoresistance. It provides brain neuroprotection by efficiently limiting the entry of exogenous molecules into brain,

while it could limit the entry of therapeutics and contributes to the development of pharmacoresistance particularly in certain conditions where its expression at the BBB is increased significantly (Miller et al., 2008).

ABCC Family—In humans, the family of multidrug resistance-associated proteins (MRPs or ABCC) has nine members involved in drug transport (Dallas et al., 2006). Among them, MRP1, 2, 4 and 5 are the most studied. MRP1, MRP2 and MRP4 have definitive localization in brain capillaries (Miller, 2014). In the CNS, MRP1 is a landmark of the blood-CSF barrier (BCSFB) because it localizes at the basolateral membrane of choroid plexus epithelial cells; it is also detected at the luminal and abluminal membranes of capillary endothelium (Daood et al., 2008; Gazzin et al., 2008; Gazzin et al., 2011; Rao et al., 1999). Moreover, MRP1 expression has been reported in human astrocytoma and glioblastoma cells obtained from epileptic patients (Decleves et al., 2002; Hirrlinger et al., 2002). However, using immunofluorescence techniques, Nies et al could not detect MRP1 in neurons or glial cells in human cerebral cortex and subcortical white matter (Nies et al., 2004). MRP2 is expressed mainly on the apical side of cell membrane of capillary endothelium while, in contrast to MRP1, its expression in BCSFB is negligible (Dallas et al., 2006). Moreover, MRP2 expression was detected in rat astrocytes (Dallas et al., 2003) as well as pericytes in culture (Yousif et al., 2007). MRP2 expression data within the human brain parenchyma is currently lacking. Mrp4 seems to be expressed on both the luminal and abluminal membranes of the rat brain capillary endothelium. Similar to P-gp, MRPs are made of two homologous and highly conserved six-transmembrane proteins interconnected by a central cytoplasmic linker domain and they are subjected to glycosylation that protects MRPs from degradation and mislocalization (Chang, 2007; Perego et al., 2010). They also contain an additional membrane-spanning domain.

ABCG2—ABCG2 or breast cancer resistance protein (BCRP) can actively extrude a broad range of endogenous and exogenous substrates. It is predominantly expressed at the luminal membrane of the BBB cells and displays substrate overlap with P-gp (Aronica et al., 2005; Maliepaard et al., 2001). However, the unique structural feature that distinguishes BCRP from other ABC transporters, including P-gp, is that it is a 72-kD half ABC transporter with only one nucleotide-binding domain and one membrane-spanning domain. It works as homodimer, possibly as heterodimer with other ABCG half transporter isoforms (Mao and Unadkat, 2015). In addition, posttranslational modifications such as glycosylation do not appear to contribute to function or membrane localization of BCRP (Diop and Hrycyna, 2005). Interestingly, whereas expression of P-gp is higher than that of BCRP in the murine BBB, recent data showed that mRNA levels of BCRP are about eightfold higher than P-gp mRNA levels in human brain capillaries (Dauchy et al., 2008; Kamiie et al., 2008). Nevertheless, BCRP is thought to act in concert with P-gp to exert a synergistic effect in limiting BBB permeability (Agarwal et al., 2011). Since its discovery in 1998, expression of BCRP has been confirmed in endothelial cells of capillaries isolated from human brain (Aronica et al., 2005), in cultured human BMEC mouse brain capillaries, immortalized rat brain endothelial cells, primary cultured rat astrocytes and rat and mouse brain microglial cells (Eisenblatter et al., 2003; Lee et al., 2007; Zhang et al., 2003). BCRP localization in neurons is controversial. Although BCRP was not observed initially in neurons of normal

subjects and epileptic patients (Aronica et al., 2005), it was detected later in neurons of stroke patients and refractory epileptic patients (Dazert et al., 2006; Lazarowski et al., 2007).

ABC efflux transporters substrates

The most remarkable feature of ABC efflux transporters is their broad substrate spectrum (Miller, 2015). Although less data are available for specific endogenous substrates, some hormones, phospholipids, cytokines, and prostaglandins are known to be effluxed. For instance, several phospholipids, sphingolipids, aldosterone, and amyloid-β (neuronal byproduct) are P-gp substrates; glutathione (GSH), GSH-conjugated leukotrienes and prostaglandins, glucoronide and sulfate conjugates are MRP1 substrates; estrones and bile acids are BCRP substrates (Sharom, 2008). In addition to endogenous molecules, ABC efflux transporters handle structurally diverse therapeutic agents that range from small drug molecules such as morphine (285 Da) to large drugs such as cyclosporine-A (1200 Da). However, it is worth noting that P-gp, BCRP and MRPs have, in part, overlapping substrates belonging to different chemical classes including chemotherapeutics, HIV protease inhibitors, opioids, antibiotics, and many more (Table 1) (Sharom, 2008). Despite their large substrate-binding pocket and wide range of substrate specificity, ABC efflux transporters show some preferences for molecules with certain physicochemical characteristics. For example, most of P-gp substrates are low molecular weight molecules (300-1000 Da) that are amphipathic, lipophilic, planar (have aromatic rings) and either neutral or cationic at physiological pH (Begley, 2004). MRPs prefer anionic substrates and conjugates, while BCRP transports both positively and negatively charged molecules and conjugated organic anions, particularly sulfated and glucuronide conjugates (Mao and Unadkat, 2015; Zhou et al., 2008). It is worth mentioning that MRP1 and MRP2 have similar substrate profiles but are distinguishable based on the degree of substrate affinity and transport kinetics, with MRP1 having higher affinity in several instances (Dallas et al., 2006; Kruh and Belinsky, 2003). Table 1 lists selected therapeutic agents that are used in the treatment of neurological disorders and are known to be substrates for efflux transporters.

Regulation of ABC efflux transporters at BBB

Evidence from numerous studies indicates that regulation of the expression and activity of ABC efflux transporters is complex, involving pre- or post-transcriptional modifications (Miller, 2015). Most of these signaling pathways that regulate expression of ABC efflux transporters in brain endothelium are activated by either surface receptors or nuclear receptors (Miller, 2014). Studies of the regulatory mechanisms of ABC efflux transporters are important to understand how BBB respond to the changes in its environment (dynamics of BBB), what are the factors that urge specific response, and the extent and the rapidity of this response. Moreover, identifying signaling pathways that regulate ABC efflux transporters in health and in neurological disorders could provide promising therapeutic targets that could be modified to change disease progression or enhance the efficacy of therapeutic agents. In the following sections, we will discuss regulatory signaling pathways that control the expression and activity of ABC efflux transporters. These pathways will be classified according to the trigger or stressor that activates them.

Inflammatory stress—Many systemic and CNS diseases, such as infections, stroke, trauma, neurodegenerative diseases, and neuroinflammation, are associated with inflammatory responses that affect the BBB (Rosenberg, 2012; Zlokovic, 2008). Inflammatory responses are mediated by proinflammatory cytokines [e.g. tumor necrosis factor-α (TNF-α), interleukins (IL-1 and IL-6)] and inflammogens [e.g., lipopolysaccharide (LPS)] that bind to endothelial cell surface receptors and trigger a wide range of changes in endothelial cell function (Chakravarty and Herkenham, 2005; Chan et al., 2011; Heneka et al., 2015; Konsman et al., 2004; Nadeau and Rivest, 1999; Nguyen et al., 2002; Rivest, 2003; von Wedel-Parlow et al., 2009). Not surprisingly, these inflammatory mediators can alter the expression and activity of ABC efflux transporters (Bauer et al., 2007; Hartz et al., 2006; von Wedel-Parlow et al., 2009). ABC efflux transporter expression and activity in brain capillary endothelial cells showed complex responses to inflammatory stress based on the time course of exposure (Figure 1) (Bauer et al., 2007; Hartz et al., 2004; Hartz et al., 2006). One of the most important inflammatory mediators that participates in the regulation of ABC efflux transporters is proinflammatory cytokine, TNF-α (Bauer et al., 2007; Hartz et al., 2004; Hartz et al., 2006). Short-term exposure of isolated rat brain capillaries (~1h) to TNF-α decreased P-gp activity without affecting its expression while, expression and activity of MRP1 and BCRP were unchanged (Hartz et al., 2004; Hartz et al., 2006). In these capillaries, TNF-α induced release of ET-1 from endothelial cells and activation of endothelin receptor-B (ETR_B) (Figure 1A) (Hartz et al., 2004). Activation of ETR_B enhanced activity of inducible nitric oxide synthase (iNOS) and protein kinase C-β1 (PKCβ1) (Hartz et al., 2006; Rigor et al., 2010; Wang et al., 2011b). PKCβ1 activates sphingosine kinase (SK), which converts sphingosine into sphingosine-1-phosphate (SIP) (Cannon et al., 2012). S1P is effluxed to extracellular space by MRP1, which has been reported to be essential for the activity of this regulatory pathway (Cartwright et al., 2013). Extracellular S1P binds to S1P receptor-1 (S1PR-1) at the cell membrane of endothelial cells and activates a signaling cascade that involves a G-protein coupled receptor and results in a rapid reduction in P-gp activity (Cannon et al., 2012).

In accordance with ET-1 signaling pathway, it has been reported that TNF-α release under inflammatory stress activates TNF receptor-1 (TNF-R1) in the cell membrane of endothelial cells and enhances ET-1 release. ET-1 is produced in endothelial cells in a proform (big-ET), which is cleaved by endothelin-converting enzyme (ECE) to the soluble active ET-1 (Figure 1) (Hartz et al., 2006). In case of infection, it has been reported that LPS binds to toll-like receptor-4 (TLR4) in brain capillary endothelial cells and enhances rapid reduction in P-gp activity through the release of TNF-α [TNF-α is produced in endothelial cells in a proform (TNF-α precursor), which is cleaved by TNF-α converting enzyme (TACE) to the soluble active TNF-α] (Hartz et al., 2006). However, it is not yet clear whether pathogen (or microbe) associated particles other than LPS [e.g. double-stranded (viral) RNA that activates TLR3 and gram-positive cell wall constituents that activate TLR2)] directly or indirectly (through TNF-α) activate ET_B receptor signaling and thereby rapidly alter P-gp activity (Bauer et al., 2007; Hartz et al., 2006; Schinelli, 2006).

Another endogenous polypeptide that could be released in response to different conditions including inflammatory stress is the vascular endothelial growth factors (VEGF) (Ferrara,

2002). Similar to ET-1, VEGF has been observed to mediate rapid, specific, and concentration-dependent reduction in P-gp transport activity in brain endothelial cells (Figure 1A) (Hawkins et al., 2010b). However, different pathways other than the PKCβ1 pathway mediate VEGF activity. In isolated rat capillaries VEGF reduces P-gp transport activity through activation of VEGF receptor-2 (VEGFR-2 or flk-1 receptor) and Src kinase (Hawkins et al., 2010b). Consistent with this, intracerebroventricular injection of low doses of VEGF in rat brain increases accumulation of the P-gp substrates, ^{3}H-morphine, and ^{3}H-verapamil. Systemic administration of a Src kinase inhibitor blocked the effects of VEGF on P-gp mediated transport (Hawkins et al., 2010b). In accordance with Src activation, it has been reported that inhibition of P-gp transport activity is associated with caveolin-1 (Cav-1) phosphorylation by Src kinase in caveolae, which provides a favorable environment for the regulation of P-gp (Figure 1A) (Jodoin et al., 2003). Moreover, transfection of rat brain endothelial cells (RBE4 cells) with Src inhibits the transport of ^{3}H-verapamil or ^{3}H-taxol by P-gp through phosphorylation of Cav-1 (Barakat et al., 2007).

Although it is not yet clear how this rapid reduction in P-gp function occurs, a recent study showed that signaling through VEGF/Src-kinase removed P-gp from the surface of the luminal plasma membrane and provided protection from proteolysis in an in vivo protease-K protection assay (Hawkins et al., 2010a). In the same study, activation of PKCβ1 provided no detectable protection, indicating no change in the cellular location of the P-gp. However, other possible mechanisms such as presence of PKCβ1 adaptor protein, covalent modification of P-gp or changes in its lipid or protein microenvironment may underlie the rapid loss of transport activity (Hawkins et al., 2010a).

In contrast to reduced P-gp activity observed after short-term exposure to inflammatory stress, several studies reported increased activity and expression of P-gp with long-term exposure (Bauer et al., 2007; Zhao et al., 2002). Bauer et al showed that long-term exposure (>6 h) of rat brain capillaries to TNF-α activates TNF-R1 and induces release of ET-1, which binds to endothelin receptor (ETR) (Figure 1B) (Bauer et al., 2007). It was suggested that both isoforms of ETR (ETR_A and ETR_B) are involved by forming a dimer, which stimulates NF-κB nuclear translocation through activation of inducible nitric oxide synthase (iNOS) and protein kinase C-β2 (PKCβ2) (Figure 1B) (Bauer et al., 2007). NF-κB is a stress-driven, master regulator of ABC efflux transporter expression at the blood–brain barrier. NF-κB is a homo- or hetero-dimer of RelA/p65, RelB, c-Rel, p50, and p52 subunits. In the cytoplasm, NF-κB dimers are held inactive by association with IκB proteins (Inhibitor of κB); this masks the nuclear localization signals of NF-κB. Phosphorylation of IκB by IκB kinase complex, leads to degradation of IκB and release of NF-κB dimer, which translocates to the nucleus, where it binds DNA consensus sequences, and alters expression of target genes (Hayden and Ghosh, 2012). In addition to TNF-α and ET-1, a wide range of soluble extracellular ligands, membrane-bound extracellular ligands as well as changes of endothelial intracellular environment (e.g. DNA damage and reactive oxygen species) appear to activate the NF-κB pathway in the brain endothelial cells.

ABC efflux transporter function and expression in endothelial cells is inhibited by the pro-inflammatory cytokines, IL-1β and IL-6. Von Wedel-Parlow et al showed that IL-1β rapidly decreases BCRP mRNA level within 6 h. However, after 24 and 48 h the mRNA levels

returned to control values. On the other hand, IL-1β caused a continuous decrease in P-gp expression but did not affect MRP (von Wedel-Parlow et al., 2009). A previous study showed that treatment of the brain endothelial cell derived from various stages of development of the guinea pig with the pro-inflammatory cytokines, IL-1β, IL-6 and TNF-α has a different effect on expression of P-gp. At late gestational stage and at postnatal stage, IL-1β, IL-6 and TNF-α exposure resulted in a dose-dependent decrease in P-gp function (Iqbal et al., 2012). Cytokine-induced reductions in P-gp function were associated with decreased ABCB1 mRNA expression (Iqbal et al., 2012). Using human endothelial cells (hCMEC/D3), Poller et al showed that BCRP mRNA levels were significantly reduced by IL-1β, IL-6 and TNF-α, while P-gp mRNA levels were slightly reduced by IL-6, but significantly increased after TNF-α treatment (Poller et al., 2010). Unlike the effect of TNF-α, the cascade of molecular steps that is activated by IL-1β and IL-6 and mediates changes in expression of P-gp and BCRP has not been defined.

Consistent with the complexity of inflammatory response, effects of proinflammatory stimuli on ABC efflux transporter expression/activity at the BBB are complex, depending on the nature of the stimulus, the dose, the time of exposure and the transporter under investigation (Miller, 2015).

Oxidative stress—Another important stressor that mediates alteration in ABC efflux transporters is oxidative stress (Miller, 2014). Felix and Barrand provided evidence for the effect of oxidative stress on the expression of P-gp at BBB endothelium (Felix and Barrand, 2002). They exposed primary cultured rat brain endothelial cells with up to 500 μM H_2O_2, causing a concentration-dependent increase in expression and activity of P-gp but not of MRP1 (Felix and Barrand, 2002). A follow up study by the same group suggested involvement of several signaling effectors including ERK1/2, PKC, Akt, JNK, and NF-κB. However, the authors did not provide any evidence for the connections between these activated proteins, although they suggested that NF-κB could play the central role in P-gp modulation (Nwaozuzu et al., 2003). Another study showed that oxidative stress, induced by sulphoraphane (SFN) administration, increases overexpression of P-gp, BCRP and MRP2 at the rat BBB via a signaling pathway that includes activation of the nuclear factor (erythroid derived 2)-like 2 (Nrf2) (Figure 2). Nrf2 is a transcription factor that regulates the expression of proteins that protect against oxidative and electrophilic stress. At the rat BBB, SFN increased P-gp, BCRP and MRP2 expression by signaling indirectly through Nrf2, p53, p38 and NF-κB (Wang et al., 2014). In addition to Nrf2 pathway, it has been reported that oxidative stress induced by diesel exhaust particles (DEPs) stimulates TNF-α release and activate TNF-R1 (Figure 2). DEPs are ultrafine particles present in diesel exhaust, one of the most common urban air pollutant (Nel, 2005). Exposure to this environmental toxin has been correlated with increased risk of fatal stroke, cerebrovascular and oxidative stress that may trigger several neurological disorders (Block et al., 2004; Calderon- Garciduenas et al., 2004; Wellenius et al., 2005). Previous studies showed that, DEPs could enter the body and reach the brain, where they cause oxidative stress and up-regulate P-gp expression (Hartz et al., 2008). In this study, Hartz et al showed that 6 hours exposure of isolated rat brain capillaries to DEPs increased P-gp, BCRP, MRP1 and MRP2 expression in a concentration-dependent manner. This study demonstrated that exposure of isolated capillaries to DEPs

activated NADPH oxidase and superoxide production. Release of reactive oxygen species (ROS) stimulates TNF-α release. Although DEP exposure caused TNF-α was released and TNF-R1 activated, there was no evidence for activation of ETR or PKC. Instead, TNF-R1 signaling activated the stress-activated protein kinase, c-Jun N-terminal kinase (JNK) (Figure 2) (Hartz et al., 2008). Consistent with Nwaozuzu et al., JNK phosphorylates and thus activates c-jun, a key component of the transcription factor activator protein-1 (AP-1), which in turn increases P-gp expression (Hartz et al., 2008; Nwaozuzu et al., 2003). Together, these findings suggest that downstream events for TNF-α release and TNF-R1 activation depend on the type of initial stressor.

Xenobiotics—Xenobiotics activate nuclear receptors in the endothelial cells of BBB and increase expression of ABC efflux transporters (Miller, 2015). Nuclear receptors are the largest known family of transcription factors that function as modulators of tissue gene expression in response to exposure to xenobiotics (Novac and Heinzel, 2004). Several nuclear receptors have been shown to regulate ABC efflux transporters (Miller, 2014). Activation of pregnane X receptor (PXR) (Bauer et al., 2006), constitutive androstane receptor (CAR) (Wang et al., 2010), arylhydrocarbon receptor (AhR) (Wang et al., 2011a) and glucocorticoid receptors (GR) (Narang et al., 2008) increases P-gp, BCRP and MRP2 expression in the brain capillary endothelium. Wide range of substrates including, but not limiting to, therapeutic agents, dietary constituents, nutraceuticals and environmental toxicants can activate these receptors (Miller, 2014; Novac and Heinzel, 2004). In addition to xenobiotics, some nuclear receptors can be activated by endogenous ligands such as steroid hormones, bile salts, and vitamins (Novac and Heinzel, 2004). This broad substrate specificity is in accordance with the function of these nuclear receptors in the activation of the proteins that are involved in the detoxification of xenobiotics from the body such as metabolizing enzymes and efflux transporters.

In their inactivated state, nuclear receptors typically reside in cytoplasm where they are bound to transcriptional corepressors that recruit specific histone deacetylase-containing complexes. The activation of nuclear receptors begins when xenobiotics permeate through the cell membrane either by selective transport or diffusion, bind to the nuclear receptor and stimulate its dissociation from the histone deacetylase-containing complex, translocating to the nucleus (Figure 3). Once in the nucleus, the ligand-receptor complex recruits coactivators and forms homodimers or, in many cases, heterodimerizes with the retinoid X receptor (RXR). These heterodimers bind to response elements in the promoter and enhancer regions of target genes and increase their transcription (Novac and Heinzel, 2004; Olefsky, 2001). To date, direct interaction of the ligand-bound nuclear receptor with promoter regions in the target transporter genes is the only known mechanism by which these receptors can activate ABC efflux transporters expression at BBB (Miller, 2015).

Although most of the nuclear receptors activate expression of P-gp, BCRP and MRP2 at BBB, there is one exception for this observation, which is related to the reported down regulation of BCRP by activation of estrogen receptor (Figure 3) (Hartz et al., 2010a; Hartz et al., 2010b; Mahringer and Fricker, 2010). Short-term exposure of male or female rat and mouse brain capillaries to estradiol (E2) rapidly and reversibly reduces BCRP transport activity without altering protein expression. Both ERα and ERβ are involved (Figure 3)

(Hartz et al., 2010b). Extended exposure to E2 for more than 6 hours decreases BCRP expression. This reduction in BCRP expression is mediated by ERβ but not ERα. To decrease BCRP expression, ERβ signals through phosphatase and tensin homolog (PTEN), phosphatidylinositide-3-kinase (PI3-K), protein kinase B (Akt), and glycogen synthase kinase-3β (GSK-3β) (Figure 3) (Hartz et al., 2010a).

Glutamate—Glutamate is an excitatory neurotransmitter that contributes to excitotoxicity in several neurological diseases. For instance, excess glutamate release occurs in amyotrophic lateral sclerosis and epilepsy and its signaling via an ionotropic, N-Methyl-D-aspartate (NMDA) receptors is a major contributor to the pathophysiology of these disorders (Barnes and Slevin, 2003). Activation of glutamate receptor NMDA has been implicated in P-gp overexpression at the BBB of epileptic patients (Bauer et al., 2008). Responses to increased levels of glutamate in the brain include NF-κB activation and nuclear translocation and consequent alteration in ABC efflux transporter expression. Glutamate binds to NMDA receptor, increases calcium entry and activates phospholipase A2 (cPLA2), produceing arachidonic acid. This metabolite is converted to prostaglandin-E2 (PGE2) by cyclooxygenase-2 (COX-2) and released to extracellular space by efflux activity of MRP, likely MRP4 (Bauer et al., 2008). Extracellular PGE2 binds to a prostaglandin E receptor 1 (EP-1R), which then signals NF-κB activation and increased P-gp expression (Bauer et al., 2008; Pekcec et al., 2009; Zibell et al., 2009).

In contrast to a well-defined effect of glutamate on P-gp expression, BCRP expression at BBB after exposure to high levels of glutamate is controversial. While Yousif et al showed a significant increase in BCRP expression at rat BBB mediated by NMDA/COX-2 cascade (Yousif et al., 2012), a recent report by Salvamoser et al showed that glutamate exposure decreased BCRP expression and activity in isolated porcine capillaries (Salvamoser et al., 2015). These authors provided evidence for the contribution of NMDA/COX-2 cascade to the down regulation of BCRP expression and activity in porcine capillaries. Moreover, using human capillaries isolated from surgical specimens of epilepsy patients, they were able to confirm a glutamate-induced down-regulation of BCRP expression and activity in human capillaries, which argued against major species differences (Salvamoser et al., 2015). In similar study, the same group showed that MRP2 expression and activity increased significantly in porcine and human BBB models after exposure to glutamate. The NMDA/COX-2 cascade was shown to be involved (Luna-Munguia et al., 2015).

Dysregulation of ABC transporters in neurological disease

A compromised BBB is associated with several neurological diseases. Disease-induced BBB changes could manifest as mild disruption in tight junctions and enhanced BBB permeability or loss of chronic barrier integrity with altered transport of molecules across BBB, brain hypoperfusion and inflammatory responses (Zlokovic, 2008). Moreover, several lines of evidence implicate dysregulation of ABC efflux transporters to the malfunctioning of the BBB during neurological diseases and suggest that ABC efflux transporters dysfunction may exacerbate neurological disease or decrease the efficacy of CNS acting therapeutics (Abbott et al., 2010; Weiss et al., 2009; Wong et al., 2013). Table 2 summarizes changes in ABC efflux transporters that are associated with neurological disorders.

Alzheimer's disease (AD)—AD is the most common cause of irreversible dementia among the elderly with a rapidly increasing socioeconomic impact (Citron, 2010). It is a progressive neurodegenerative disorder with a complex pathogenesis that involves two well-defined pathologies, amyloid-β (Aβ) and tau-related neuropathologies (Selkoe, 2001). During the last decade, the role of ABC efflux transporters in the pathology of AD has been recognized (Cirrito et al., 2005; Qosa et al., 2014a; Rapposelli et al., 2009). Several studies have suggested ABC efflux transporters to play a pivotal role in the clearance of Aβ from the brain across BBB (Abuznait and Kaddoumi, 2012; Wolf et al., 2012). Consistent with its suggested role in Aβ clearance, a significant negative correlation exists between the densities of senile plaque lesions and P-gp levels in brain capillaries of patients with AD (Vogelgesang et al., 2002). In addition to this clinical study, P-gp was implicated to function as an Aβ efflux pump in several in vivo and in vitro studies (Cirrito et al., 2005; Kuhnke et al., 2007; Qosa et al., 2014a; Tai et al., 2009). Interestingly, using ^{11}C-verapamil and positron emission tomography imaging, a clinical study showed significant reduction in P-gp activity in AD patients compared to cognitively normal subjects (van Assema et al., 2012). Another study detected 25% lower P-gp protein expression levels in hippocampal blood vessels in post-mortem brain samples from AD patients than in samples from age-matched non-demented patients (Wijesuriya et al., 2010). Moreover, isolated brain capillaries from transgenic hAPP-overexpressing mouse model (Tg2576 mice) showed a 70% decrease in P-gp transport activity and a 60% decrease in P-gp protein expression compared to age-matched wild-type mice (Hartz et al., 2010c). Although the molecular mechanism underlying this down regulation of P-gp is not clear, some studies pointed at Aβ accumulation as a causative factor (Carrano et al., 2011; Kania et al., 2011; Park et al., 2014; Qosa et al., 2014b). Park et al showed that $A\beta_{42}$ mediates P-gp down regulation in murine brain endothelial cells (bEnd3 cells) by activation of receptor for advanced glycation end products (RAGE). The authors suggest that activation of RAGE by $A\beta_{42}$ would enhance NF-κB activity that decreases P-gp expression (Park et al., 2014). Similarly, Kania et al showed that, exposure of immortalized human brain endothelial cell line (hCMEC/D3) to Aβ peptides reduced P-gp expression with more definitive and consistent effect produced by $A\beta_{42}$ than $A\beta_{40}$ (Kania et al., 2011). Authors of this study suggested reduction in the activity of the Wnt/β-catenin pathway by Aβ exposure in the brain endothelial cells (Kania et al., 2011). Consistent with this finding, recent study demonstrated that the expression of P-gp in human BBB cells is controlled by a cross-talk between the Wnt/GSK3 canonical pathway and the Wnt/RhoA/RhoAK non-canonical pathway. Increased activity of Wnt/GSK3 canonical pathway reduced GSK3-mediated phosphorylation and ubiquitination of β-catenin, decreasing its proteasomal degradation, enhances its nuclear translocation, and increases P-gp expression (Pinzon-Daza et al., 2014). Similarly, RhoA activation through non-canonical Wnt3/RhoA/RhoAK pathway reduced the activity of GSK3. The active RhoA increases the activity of RhoAK, which induces the phosphorylation of protein tyrosine phosphatase-1B (PTP1B). After this phosphorylation, PTP1B dephosphorylates GSK3 and inactivates it (Pinzon-Daza et al., 2014).

Similar to P-gp, several studies also confirm the role of BCRP in Aβ extrusion at the BBB. Optical imaging analyses of live animals showed that Bcrp-null mice significantly accumulated more Aβ in their brains than wild-type mice (Xiong et al., 2009). Moreover, in

vitro studies utilizing BCRP overexpressing cells demonstrated BCRP to restrict the apical-to-basolateral permeability of Aβ isoforms (Candela et al., 2010; Do et al., 2012; Tai et al., 2009). However, unlike P-gp, studies of BCRP expression in the brain of AD patients showed conflicting results. Xiong et al showed that ABCG2 gene was significantly up-regulated in the brains of AD and CAA patients compared to age matched control group and the same applies to the Tg3x mouse model of AD against its matched littermate control (Xiong et al., 2009). On the other hand, Wijesuriya et al reported lack of difference in BCRP expression in the brain vasculature of AD compared to normal cases (Wijesuriya et al., 2010). Xiong et al have suggested BCRP up-regulation in the brains of AD patients as a protective mechanism during oxidative stress and inflammatory response by inhibiting the NF-κB signaling pathway, leading to decreased expression of interleukin-8 and growth-related oncogene (GRO) inflammatory genes (Xiong et al., 2009). Among the ABCC subfamily, only MRP1 has been linked to AD (Krohn et al., 2011). In a mouse model of AD that is null for the Abcc1 gene (APP/PS1×Abcc1−/−), cerebral Aβ levels increased without changes in the expression of most enzymes that would favor the production of Aβ from APP. Moreover, treatment of APP/PS1 mice with the Abcc1 gene inducer, thiethylperazine reduced brain Aβ levels (Krohn et al., 2011).

Amyotrophic lateral sclerosis (ALS)—ALS is a fatal, progressive neurodegenerative disorder that affects upper and lower motor neurons with poor prognosis. The pathogenesis of the disease is complex and involves different pathological lesions in the brain and spinal cord that are incompletely understood (Pratt et al., 2012). Recently, several reports showed evidence of BBB disturbances in the brain of ALS patients carrying the SOD1 mutation and in postmortem brains of sporadic ALS patients (Garbuzova-Davis and Sanberg, 2014). Our previous study showed a significant increase in the expression of P-gp and BCRP but not MRPs (1, 2, 4, and 5) in the spinal cords of patients and mouse models of ALS (mutant SOD1-G93A and mutant TDP43-A315T mice) (Jablonski et al., 2012). Interestingly, the increase in P-gp and BCRP expression was observed only in cerebral cortex and spinal cord while cerebellum and systemic expression of these transporters did not change (Jablonski et al., 2012). Highlighting the clinical significance of the overexpression of drug transporters in ALS, several reports confirmed that, riluzole, the only FDA-approved drug for the treatment of ALS, and other investigational ALS therapeutics are P-gp and BCRP substrates (Jablonski et al., 2014; Milane et al., 2007). Therefore, this ALS-acquired and CNS-specific overexpression of P-gp and BCRP could contribute significantly to the development of drug pharmacoresistance in ALS. In a proof-of-concept study using ALS mouse model, systemic administration of elacridar (P-gp/BCRP inhibitor) significantly increased riluzole concentrations in the brain and spinal cord and prolonged mouse survival (Jablonski et al., 2014). However, data about the regulation of P-gp and BCRP expression in ALS is still lacking and further investigations are needed to understand the mechanisms underlying this ALS-acquired and CNS-specific up-regulation of P-gp and BCRP.

Brain tumors—Brain tumors are devastating pathologies considered among the most lethal types of all cancers. Brain tumors can be divided into two categories: primary brain tumors and metastatic brain tumors. Primary brain tumors arise from the constituent cells of the brain or their meningeal covering, whereas metastatic brain tumors are secondary tumors

that metastasize from a distant site (Agarwal et al., 2011; Kamar and Posner, 2010; Parrish et al., 2015). Despite extensive research, treatment of brain tumors has been largely ineffective and systemically administered chemotherapeutic drugs show poor efficacy. This low efficacy is at least partly due to overexpression of ABC efflux transporters P-gp, BCRP and MRPs in tumor cells (Deeken and Loscher, 2007; Parrish et al., 2015). Up-regulation of P-gp, BCRP, and MRP1 has been reported in a number of neuroblastomas, astrocytomas, and glioblastomas, suggesting their contribution in generating resistance toward a number of therapeutic substrates (Agarwal et al., 2011; Haber et al., 2006; Regina et al., 2001; Wang et al., 2012). In addition to tumor cells, several studies showed that the expression of P-gp, BCRP and MRPs is also altered in the endothelial cells that form the vasculature around tumors (blood-tumor barrier) compared with normal brain vasculature (Agarwal et al., 2011; Deeken and Loscher, 2007; Parrish et al., 2015; Regina et al., 2001). For instance, P-gp expression in the blood vessels supplying brain melanoma metastases and lung metastases (metastatic brain tumors) were only 5% and 40% of that seen in normal brain tissue (Regina et al., 2001). Similarly, in primary brain tumors, Becker et al showed diminished level of P-gp in the vasculature of malignant gliomas compared with normal brain vasculature, whereas Toth et al found no difference between the P-gp expression in glioma tumor vasculature and normal tissue (Becker et al., 1991; Toth et al., 1996). Concerning MRPs Haga et al found no difference in the expression level of MRP2 between normal brain and malignant glioma cells (Haga et al., 2001). However, they did find increased expression of MRP1 in the endothelial cells forming the vasculature around tumor sites. In contrast, Pilorget et al demonstrated that P-gp is up-regulated in brain EC isolated from brain tumors compared with normal brain EC (Pilorget et al., 2007). Moreover, in this study authors provided evidence for activation of SK-1 and its product S1P to modulate P-gp transport activity in the rat brain endothelial cell line RBE4. It is worth noting that, in addition to ABC efflux transporters alterations at blood-tumor barrier, the integrity of this barrier is also compromised. Thus, the BBB is less intact in the core of primary and metastatic brain tumors compared with the normal brain vasculature. However, this disruption was seen in the site of tumor, while the vasculature remains grossly intact in other brain regions (Deeken and Loscher, 2007; Parrish et al., 2015).

Creutzfeldt-Jakob's disease (prion disease)—Creutzfeldt-Jakob's disease (CJD) is a rare, neurodegenerative, invariably fatal brain disorder, also known as prion disease (Ironside and Head, 2008). This disease is characterized by the accumulation of an abnormal isoform (PrP^{Sc}) of the prion protein (PrP) which forms aggregates responsible for the pathological progress of this disease (Ironside and Head, 2008). Like HD, studies about the involvement of P-gp and other ABC efflux transporters are lacking in CJD. Only one report by Vogelgesang et al showed that P-gp expression within endothelial cells of brain vessels is significantly lower in CJD patients than in age-matched control cases (Vogelgesang et al., 2006). In this study, authors could not detect any immunohistochemically PrP in the blood vessels of CJD patients, which raises the question of whether reduction the P-gp expression in the endothelium is the cause or the consequence of the prion disease process.

Epilepsy—Epilepsy is a neurological disorder characterized by recurrent seizures. It is one of the most common neurological disorders and affects approximately 1-2% of the world's

population (Ahmed, 2005; Kotsopoulos et al., 2005). Although several antiepileptic drugs (AEDs) have been developed and are in clinical use, about 40% of the patients failed to respond to AEDs treatment due to the development of pharmacoresistance (Loscher and Potschka, 2005c). Enhanced efflux of AEDs at the BBB due to overexpression of ABC efflux transporters is considered one of the major mechanisms underlying AEDs pharmacoresistance (Loscher and Potschka, 2005a). The first evidence for the role of ABC efflux transporter in AEDs pharmacoresistance was provided by Tishler et al who detected high expression of P-gp in the capillary endothelial cells isolated from the brain tissue of refractory epileptic patients (Tishler et al., 1995). Since then, overexpression of P-gp and other ABC efflux transporters such as BCRP and MRP have been confirmed by in vitro, in vivo and clinical studies (Aronica et al., 2012). Consistent with these findings, numerous in vivo and in vitro studies showed that many AEDs are substrates for ABC efflux transporters (Luna-Tortos et al., 2008). Moreover, co-administration of ABC efflux transporters inhibitors significantly enhanced brain penetration and efficacy of AEDs (Brandt et al., 2006; van Vliet et al., 2006). Over the past 10 years, numerous studies have been performed to understand the regulatory mechanisms that stand behind the development of pharmacoresistance against AEDs. One hypothesis that has been addressed by several studies suggested constitutive or inherited overexpression of P-gp. However, there is still substantial controversy about the validity of this hypothesis due to poor correlation between polymorphisms in the ABCB1 gene and drug-response in epileptic patients (Kim et al., 2009; Siddiqui et al., 2003; Sills et al., 2005; Tan et al., 2004).

Recent in vitro and in vivo studies have suggested that overexpression of ABC efflux transporters is complex and involves several elements of pathological alterations observed in epilepsy such as inflammatory responses, oxidative stress, ligand-activated nuclear receptors and glutamate (Potschka, 2010b). In accordance with high glutamate levels in epileptic brain, it has been shown that seizures induce overexpression of P-gp at the level of the BBB in endothelial cells through glutamate by an NMDA receptor and COX2-dependent mechanism (Bauer et al., 2008). Consistent with this sequence, the role of COX2 in regulating P-gp expression has been confirmed in different experimental models of epilepsy and inhibiting elements of NMDA/COX2 signaling pathway such as prostaglandin-E2 receptor (EP1) improves efficacy of certain AEDs (Pekcec et al., 2009; van Vliet et al., 2010).

Finally, treatment with AEDs could induce pharmacoresistance in epilepsy. Although several in vitro and in vivo studies showed the potential of AEDs to enhance expression of ABC efflux transporters, the data are still controversial (Aronica et al., 2012). In addition, because overexpression of ABC efflux transporters has been reported in the brain of epileptic patients before exposure to AEDs, it is not likely that treatment with AEDs per se is responsible for the observed pharmacoresistance (Sisodiya et al., 1999).

HIV-1 encaphelitis—Human immunodeficiency virus (HIV) is an enveloped retrovirus that causes the acquired immunodeficiency syndrome (AIDS) (Douek et al., 2009). HIV can penetrate the brain in early course of infection and causes HIV-encephalitis that is associated with chronic neuroinflammation (Gonzalez-Scarano and Martin-Garcia, 2005). Brain autopsy tissues from patients with HIV encaphilitis have increased P-gp expression in glial

cells (Hayashi et al., 2005). This results is consistent with the findings that viral protein (gp120, Tat) enhance secreation of cytokines (IL-6, IL-1β and TNF-α), which in turn can enhance P-gp expression in the brain endothelium and astrocytes (Ronaldson and Bendayan, 2006). In contrast, some studies showed that HIV has downregulatory effect on P-gp expression mediated by IL-6 and NF-κB pathway (Ashraf et al., 2011). In addition to P-gp, increased expression of MRP1 has been detected in cultured astrocytes after treatment with Tat and gp120 proteins (Hayashi et al., 2006; Ronaldson and Bendayan, 2008). This increase in MRP1 expression was suggested to be stimulated by released TNF-α and mediated by NF-κB pathway (Ronaldson and Bendayan, 2008). In addition to viral proteins, it has been reported that antiretroviral drugs can also increase expression of P-gp and mediate the development of pharmacoresistance in HIV encaphelitis. Two HIV protease inhibitors, atazanavir and ritonavir, activate CAR and PXR nuclear translocation in human endothelial cells (hCMEC/D3) and in primary culture of human brain endothelial cells which in turn enhances P-gp expression (Chan et al., 2013; Zastre et al., 2009). Moreover, a recent study suggested that other antiretroviral drugs such as maraviroc, vicriviroc and elavitegravir can modulate P-gp and/or BCRP expression (Zembruski et al., 2011).

Mental disorders—Depression and schizophrenia are the most common mental disorders that inflict the life of more than 350 and 24 millions people worldwide, respectively (Battle, 2013). Depression is a mood disorder that causes a persistent feeling of sadness, loss of interest and interferes with the ability to work, sleep, study, eat, and enjoy life (Driessen and Hollon, 2010). Schizophrenia is a severe brain disorder characterized by abnormal social behavior, failure to recognize what is real, hallucinations, delusions, and extremely disordered thinking (van Os and Kapur, 2009). The causes of these mental disorders are still unclear with complex pathogenesis that triggered by several genetic, clinical, enviromental and social factors (Battle, 2013). Changes in the ABC efflux transporters at the BBB in mental disorders are understudied with only few studies that suggested local changes of P-gp function in the brain of depressive or schizophrenic patinets . (de Klerk et al., 2009; de Klerk et al., 2010). Using positron emission tomography, a significantly lowered ^{11}C-verapamil uptake (indicating increased P-gp activity) in prefrontal cortex and temporal lobes was found in patients with a major depressive episode. Moreover, this significant decrease in ^{11}C-verapamil uptake was found in a subset of patients diagnosed with treatment-resistant depressive disorder. In addition, the same group of researchers reported a similar increase in P-gp activity in the brains of schezophrenic patients (de Klerk et al., 2010). Using positron emission tomography, patients with chronic schizophrenia under treatment with antipsychotic drugs showed a significant decrease in ^{11}C-verapamil uptake in the temporal cortex, the basal ganglia, and the amygdala, and a trend towards a significant decrease was seen throughout the brain compared with healthy controls (de Klerk et al., 2010). This decrease of ^{11}C-verapamil uptake in the brain of depressive and schizophrenic patients may be correlated with an increased activity of the P-gp pump. These results suggested a local increase in the activity and or expression of P-gp at areas that are mostly affected by depression and schezophrenia. Moreover, clinical findings of these studies speculated that pharmacoresistance in depression and schezophrenia may in fact be associated with increased P-gp function that may cause low uptake of antipsychotics (de Klerk et al., 2009). However, it is still unclear wheather the observed increase in P-gp activity in depression and

schezophrenia is related to specific pathological alterations in these diseases or to the drugs used in the treatment of these diseases (de Klerk et al., 2009; de Klerk et al., 2010).

Multiple sclerosis—Multiple sclerosis (MS) is chronic inflammatory disease in which the myelin covers of nerve axons in the brain and spinal cord are damaged. Neuropathologically multiple focal demyelinated lesions scattered throughout the CNS characterize MS. These lesions disrupt the ability of parts of the nervous system to communicate, resulting in a wide range of signs and symptoms including physical, mental, and sometimes psychiatric problems (Frohman et al., 2006). Recent studies show a decreased endothelial P-gp expression in MS, whereas endothelial BCRP, MRP1 and MRP2 were unchanged (Kooij et al., 2010; Kooij et al., 2011). Loss of vascular P-gp function during MS neuroinflammation may disturb brain homeostasis and thereby aggravate disease progression via exposure of vulnerable CNS cells to detrimental compounds. Authors of this study identified a crucial role for activated CD4+ T cells in endothelial P-gp down-regulation via intracellular adhesion molecule-1 and NF-κB signaling (Kooij et al., 2010). On the other hand, both active and inactive multiple sclerosis lesions were associated with an increase in astrocytic P-gp, MRP1 and MRP2 but not BCRP expression. The authors suggested that, TLR-3 activation of astrocytes by TNF-α led to increased P-gp and MRP1 activities (Kooij et al., 2011).

Parkinson's disease—Parkinson's disease (PD) is the second most common neurodegenerative disease that mainly affects the motor system. It is characterized by progressive loss of nigral dopaminergic neurons and formation of Lewy bodies. Although, most cases of PD are idiopathic, many studies have implicated the accumulation of environmental neurotoxins and lack of efficient brain detoxification to the development of PD (Kalia and Lang, 2015). Because impaired function of drug transporters may be associated with brain accumulation of neurotoxins, genetic polymorphism in MDR1 gene has been suggested as a risk factor for PD (Liu et al., 2013; Zschiedrich et al., 2009). Moreover, reduction in the expression of P-gp has been reported in the endothelial cells of postmortem PD patients (Westerlund et al., 2008). Consistent with that finding, positron emission tomography measurements of brain uptake of ^{11}C-verapamil, which is normally extruded from the brain by P-gp, showed significantly elevated uptake of ^{11}C-verapamil in the midbrain of PD patients relative to controls (Kortekaas et al., 2005). These studies confirmed the reduction in P-gp expression at the BBB of PD patients and loss of one important neuroprotective component of the barrier.

Stroke and ischemic brain injuries—Stroke is the third leading causes of death and disability in the world (Truelsen and Bonita, 2009). It occurs when blood flow to an area of brain is cut off due to a blocked blood vessel or bleeding in the brain. Approximately 85% of all strokes are ischaemic and 15% haemorrhagic. Ischaemic stroke is a complex pathophysiological process that triggers a cascade of biochemical and molecular events, finally causing an impairment of BBB integrity (Dirnagl et al., 1999). It has been reported that ABC efflux transporters at the BBB exhibit profound expressional changes in the brain capillaries of the ischaemic brain that have functional implications (Patak and Hermann, 2011). BBB P-gp expression and activity is elevated three hours following transient

intraluminal middle cerebral artery occlusion (MCAO). The observed overexpression of P-gp was persistent up to 24 hours after reperfusion, independent of the severity of the ischaemic event and observed also in newly generated capillaries 14 days post-stroke (Cen et al., 2013; Dazert et al., 2006; Hermann et al., 2006; Ueno et al., 2009). In contrast only a few studies have investigated the role of other ABC efflux transporters at the BBB after brain ischaemia. In mice that underwent MCAO for 90 or 30 min, Kilic et al showed that the levels of MRP1 in the brain endothelium declined 3 hours after ischaemia and recovered partly within 72 hours (Kilic et al., 2008). Regarding BCRP, Dazert et al showed increased in BCRP mRNA and protein levels 3 to 14 days post-ischemic injury (Dazert et al., 2006).

Little is known about their mechanisms that regulate ABC transporter expression in cerebral ischaemia. Since hypoxia is a major factor contributing to ischemic injury, previous study investigated the role of hypoxia inducible factors (HIF)-dependent signaling in the ischemia-induced overexpression of P-gp and MRP1 in an in vitro model of human brain endothelial cells (hCMEC/D3) (Patak et al., 2011). However, no changes in P-gp or MRP1 levels were detected in this study, despite a strong induction of HIF in the hCMEC/D3 cells, suggesting that HIF might not be essential for ABC efflux transporters regulation in endothelial cells (Patak et al., 2011). Authors of this study suggested that the overexpression of both transporters seen in previous studies after cerebral ischaemia could depend on other factors than hypoxia alone that are associated with ischaemia and have been described to induce P-gp expression, such as glucose depletion (Ledoux et al., 2003), reactive oxygen species that are generated by reoxygenation following hypoxia as shown in rat brain endothelial cells (Li and Jackson, 2002; Robertson et al., 2009; Robertson et al., 2011) or glutamate that is released during brain ischaemia (Zhu and Liu, 2004). Moreover, recent studies provided evidence for P-gp and BCRP regulation by ApoE in response to ischemia (ElAli and Hermann, 2010). Using brain microvascular extracts, the authors indicated that P-gp mRNA increased in ischaemic cerebral microvessels of wild-type, but not ApoE−/− mice, whereas MRP1 mRNA was increased in the ischaemic brain capillaries of ApoE−/−, but not wild-type mice.

Conclusions

ABC drug efflux transporters are important elements of the BBB. Regulation of expression and activity of these transporters are complex processes that are affected by numerous pathophysiological stressors, such as inflammatory and oxidative stress and xenobiotics. A primary function of ABC efflux transporters at BBB is to move molecules, both endogenous and xenobiotics, out of the CNS (You and Morris, 2006). Although these transporters play an important role in providing neuroprotection, their wide range substrate specificities grants them the potential to recognize many therapeutic drugs targeted at the CNS (Miller, 2015). As a consequence, these ABC efflux transporters play a significant role in governing bioavailability, therapeutic efficacy, pharmacokinetics and most importantly brain disposition of a variety of drugs, thereby governing drug efficacy and significantly contributing to the development of pharmacoresistance (Loscher and Potschka, 2005b; Miller, 2015; Sharom, 2008). Therefore, ABC efflux transporters could have two contradictory effects on the development and progression of neurological diseases: On the

one hand, they protect the CNS by promoting detoxification, but they also constitute an obstacle to brain penetration, diffusion and bioavailability of CNS therapeutics.

Several approaches have been used to decrease the activity of ABC efflux transporters, mainly P-gp, in neurological disorders such as epilepsy (Potschka, 2010a). Transient inhibition of ABC efflux transporters by using direct inhibitors may be a useful strategy to reverse or prevent pharmacoresistance due to overexpression of such transporters. Various inhibitors of P-gp, BCRP and MRPs have been developed, however, most of these inhibitors lack specificity and inhibit several ABC efflux transporters; they also exhibit side effects at high concentrations (Figure 4). Moreover, according to the fact that P-gp and BCRP act synergistically in limiting drug entry to the brain, the use of dual inhibitor that could inhibit both P-gp and BCRP has the potential to dramatically increase the brain accumulation of drugs that are dual substrates. In this regard, previous studies reported about 70-fold increase in the brain distribution of gefitinib (anticancer agent) in Mdr1(−/−) Bcrp(−/−) mice (Agarwal et al., 2010). Therefore, direct inhibitors (such as elacridar or tariquidar) could enhance significantly brain levels of centrally acting drugs.

In contrast, results from several reports showed that increasing expression of P-gp could significantly enhance the extrusion of Aβ from the brain across BBB (Abuznait et al., 2013; Brenn et al., 2014; Hartz et al., 2010c; Qosa et al., 2012). However, further pre-clinical and clinical studies are needed to prove the validity of this approach and whether it could be generalized for other ABC efflux transporters and other diseases.

When targeting ABC efflux transporters by inducers or inhibitors, one should take into account the effects of long-term modulation on the transporters' protective function as well as the potential of development of pharmacoresistance. One must be mindful of not impairing brain clearance of potentially toxic metabolites and proteins when inhibiting efflux transporters and of not developing pharmacoresistance with inducers or with disease targeting drugs that also act as inducers (PXR and CAR activators). Finally, changes in the expression and activity of ABC efflux transporters in neurological diseases might result from complex interacting factors, such as progression of disease, alterations in target sites and changes in the expression of other proteins. Therefore, successful targeting of ABC efflux transporters in the treatment of neurological diseases requires further studies to understand the specific mechanisms that regulate individual ABC efflux transporters.

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Highlights

- ABC efflux transporters are important element of BBB.
- ABC efflux transporters provide neuroprotection against several neurotoxins.
- ABC efflux transporters contribute to the pharmacoresistance against CNS drugs.
- Several stressors modulate the activity of ABC efflux transporters at BBB.
- Pathological alterations of ABC efflux transporters are associated with many CNS disorders.

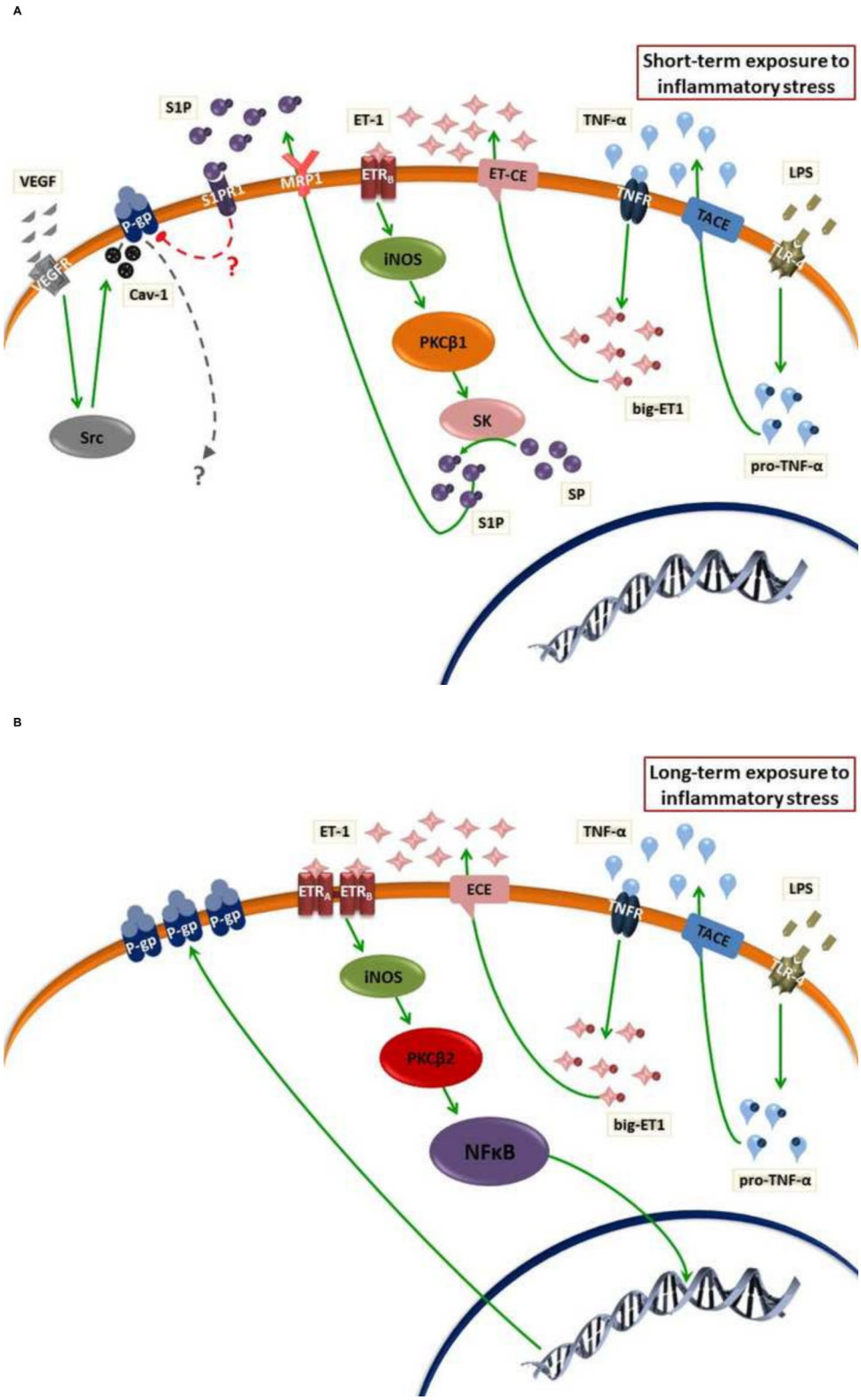

Figure 1.

(A) Effect of short-term exposure to inflammatory stress on ABC efflux transporter activity and expression in the endothelium of BBB. ET-1 and VEGF enhance rapid reduction in the activity of P-gp through activation of PKCβ1 and Src kinase, respectively. (B) Long-term exposure to inflammatory stress enhances increased P-pg expression through PKCβ2 and NF-κB pathway. In both pathways, TNF-α or LPS could stimulate ET-1 release. While BCRP and MRP1 activity and expression did not change upon short-term exposure to inflammatory stress, only BCRP expression decreased after long-term exposure. However, the cascade of molecular steps that mediates reduction in BCRP expression has not been defined.

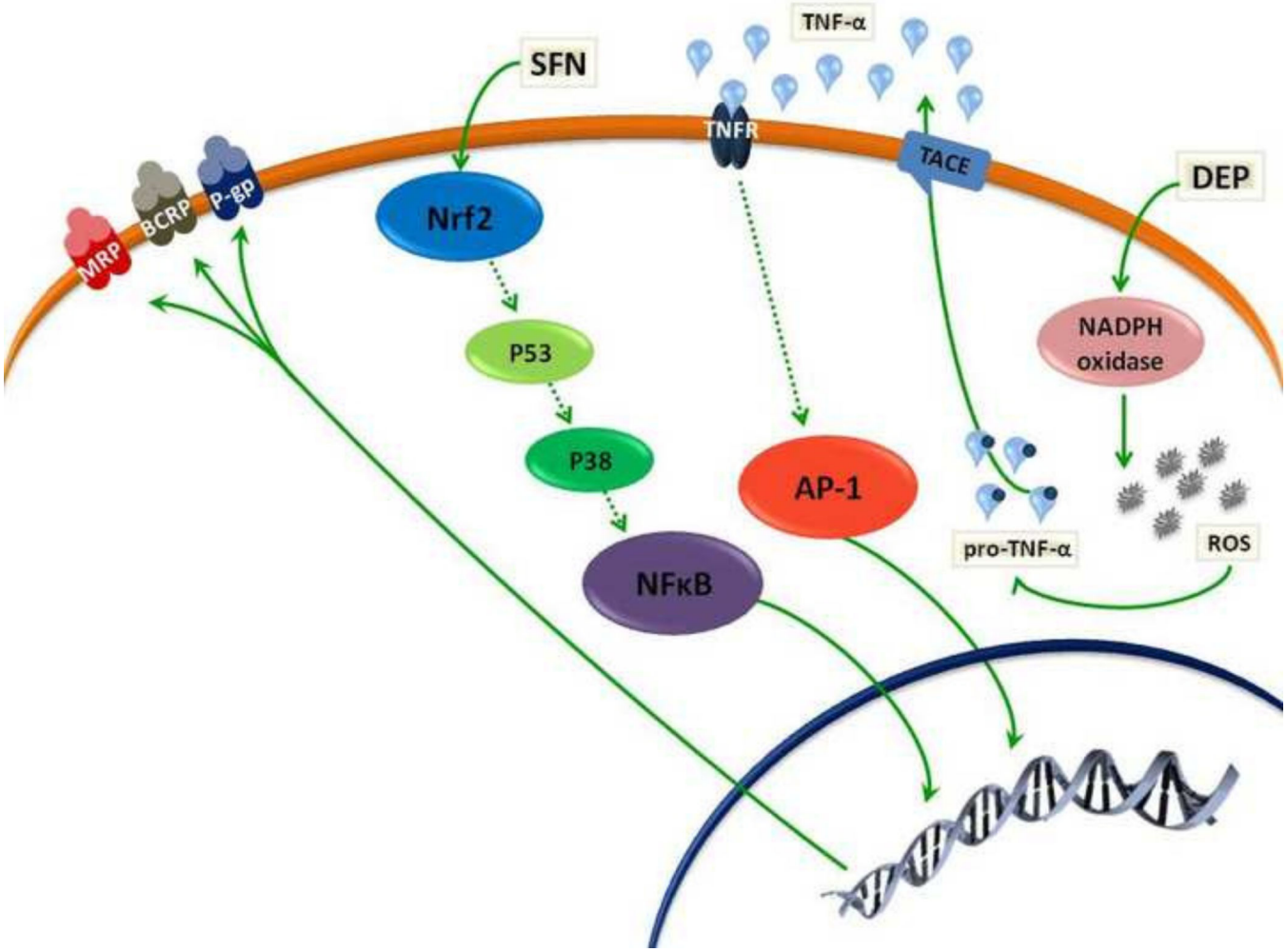

Figure 2.

Oxidative stress induces ABC efflux transporter expression. SFN activates an Nrf2 signaling pathway that includes P53, P38 and NF-κB activation. DEP activates NADPH oxidase that releases ROS. ROS stimulates TNF-α release that activates AP-1 transcription factors through activation of TNF-R1. In DEP-driven oxidative stress, TNF-R1 activates pathways that do not involve NF-κB.

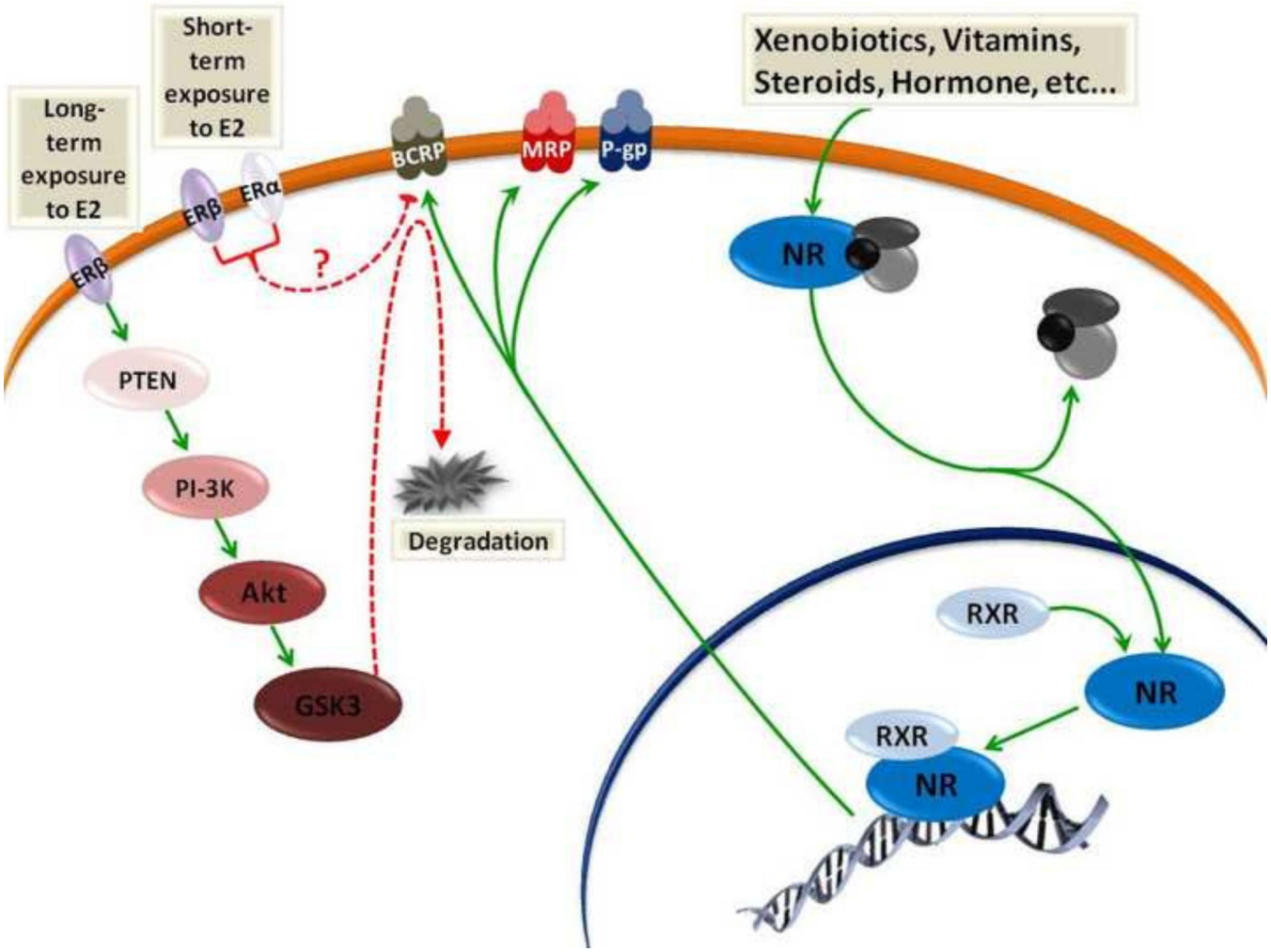

Figure 3.

Nuclear receptor activation by xenobiotics or other endogenous ligands enhances release of nuclear receptors from co-suppressors and translocation into the nucleus where they form homodimers or heterodimers with RXR to stimulate ABC efflux transporter expression. Short-term exposure to estradiol (E2) reduces BCRP activity rapidly through activation of ERα and ERβ, while long-term exposure to E2 activates ERβ, which stimulates BCRP degradation and through PTEN/PI-3K/Akt/GSK3 dependent pathway.

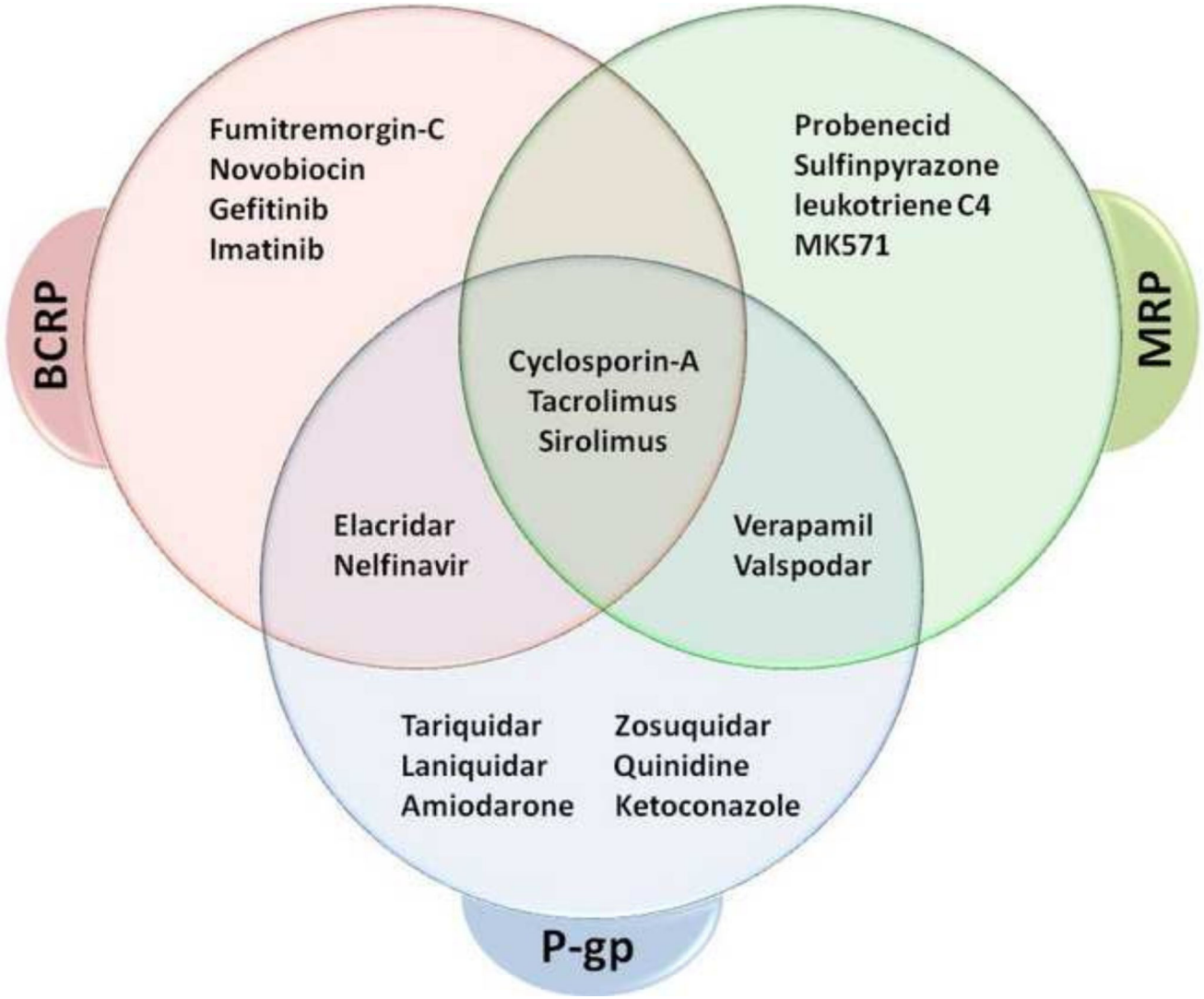

Figure 4.
Venn diagram shows common inhibitors for P-gp, BCRP, MRP1 and MRP2.

Table 1

List of selected clinically relevant ABC efflux transporters substrates

Drug Class	P-gp	BCRP	MRPs
ALS drug	Riluzole	Riluzole	
Analgesics	Morphine		
	Methadone		
	Fentanyl		
Antibiotics	Erythromycin	Ciprofloxacin	Azithromycin
	Gramicidin A	Ofloxacin	Ciprofloxacin
	Rifampicin	Norfloxacin	Difloxacin
Anticancer	Etoposide	Etoposide	Etoposide
	Irinotecan	Irinotecan	Irinotecan
	Vinblastine	Methotrexate	Vinblastine
	Vincristine	Imatinib	Vincristine
	Temozolomide	Erlotinib	Methotrexate
	Imatinib	Gefitinib	Cisplatin
	Gefitinib	Mitoxantrone	Imatinib
			Gefitinib
Antidepressant	Amitryptiline		
	Nortryptiline		
	Doxepin		
	Venlafaxine		
	Paroxetine		
Antidiarrheal	Loperamide		
Antiemetic	Ondansetron		
	Domperidone		
Antiepileptics	Felbamate		Levetiracetam
	Topiramate		Phenobarbital
	Phenytoin		
	Phenobarbital		
	Lamotrigine		
	Levetiracetam		
	gabapentin		
Antihelminthic	Ivermectin		
	Abamectin		
Antihistamine	Fexofenadine		
Cardiovascular agents	Reserpine		
	Propronalol		
	Verapamil		
	Nifedipine		
	Diltiazem		
	Digoxin		

Drug Class	P-gp	BCRP	MRPs
	Quinidine		
	Amiodarone		
	Lovastatin		
	Simvastatin		
Corticosteroids	Dexamethasone		
	Hydrocortisone		
	Corticosterone		
	Cortisol		
	Aldosterone		
HIV drugs	Ritonavir	Zidovudine	Ritonavir
	Indinavir	Lamivudine	Indinavir
	Saquinavir		Saquinavir
	Amprenavir		Nelfinavir
	Nelfinavir		Zidovudine
	Lopinavir		
Immunosuppressant	Cyclosporine-A	Cyclosporine-A	Cyclosporine-A
	Tacrolimus	Tacrolimus	Tacrolimus
	Sirolimus	Sirolimus	Sirolimus
		Reserpine	
		Prazosin	

Table 2

Summary of changes in ABC efflux transporters activity in neurological disorders

Disease	P-gp	BCRP	MRP1	MRP2
Alzheimer's disease	↓	↔	↓	?
Amyotrophic lateral sclerosis	↑	↑	↔	↔
Brain tumors	↓	?	↑	↔
Creutzfeldt-Jakob disease	↓	?	?	?
Depression	↓	?	?	?
Epilepsy	↑	↑	↑	↑
HIV-encephalitis	↔	↑	↑	?
Multiple sclerosis	↓	↔	↔	↔
Parkinson's disease	↓	?	?	?
Schizophrenia	↓	?	?	?
Stroke and ischemic brain injuries	↑	↑	↑	?