ISSN 1669-5402 (Print) ISSN 1669-5410 (Online)

Physiological Mini-Reviews

Edited by the Argentine Physiological Society.

Vol. 2, N° 3, October 2006.

http://www.mini.reviews.safisiol.org.ar

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[ISSN 1669-5402 (Print); ISSN 1669-5410 (Online)]

Edited by the **Argentine Physiological Society**

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http://www.mini.reviews.safisiol.org.ar

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(Resol. IGJ 763-04)

Clinical and experimental evidences for a role of ABC transporters in the mechanisms underlying multidrug resistance in epilepsy.

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Epilepsy is a common neurological disorder affecting 1-2% of the general population. Although antiepileptic therapies efficiently control seizures in most patients, it is estimated that 20-25% of the affected population fails to achieve good control with antiepileptic drug (AED) treatment, thus defining refractory epilepsy (RE) (1). Although the underlying mechanisms involved in AED resistance are poorly understood, it has been suggested that unresponsiveness to AEDs resembles the mechanism of resistance to chemotherapy in cancer. Considerable progress has bee attained recently in elucidating the molecular mechanisms of refractoriness during cancer chemotherapy. The foundational finding was that tumor cells become refractory to chemotherapeutic agents due to the action of the P-glycoprotein (P-gp), the product of the MDR-1 gene. P-gp acts as energy-dependent pumps that extrudes potentially toxic compounds out of the cells and can confer resistance levels of 1000-fold or more to the expressing cells (2,3).

P-gp and multidrug resistance associated proteins (MRP).

Biochemical, molecular, and structural analysis have definitively established that

the involvement of Pgp in pharmacoresistance results from its primary function as an ATP- and Ca^{2+}-dependent detoxifying pump.

It is know well admitted that multi-drug resistance (MDR), once established, is a multifactorial phenomenon that cannot be attributed solely to P-gp over-expression. To date, MDR is conferred by distinct proteins that belong to one large superfamily of proteins known as ABC transporters, (named for their distinctive domains that bind ATP). The multi-drug-resistance-associated proteins (MRP1-7) and the breast cancer resistant protein (BCRP) have been associated with MDR phenotype (4).

The normal brain expresses P-gp in the vascular endothelial cells (VEC) of the blood brain barrier (BBB), and choroids plexus, where it is believed to contribute to the blood-cerebrospinal fluid barrier (5). The P-gp expression in capillary luminal membranes of VEC actively pumps certain of these substrates back into blood, thus limiting their brain penetration and reducing the amount of AEDs available for the brain parenchimal cells, particularly to epileptic neurons.

MDR-1 and MRP-1 in clinical refractory epilepsy.

About one-half of newly diagnosed patients with epilepsy obtain full seizure control with the first AED tried, and 13% more enter remission with the addition of a second drug. The remaining patients are not likely to obtain satisfactory seizures control with any single drug or drug combination. Why a subgroup of patients repeatedly fails to control the seizures with one AED after another? (6). **- 19 -**

These data, indicates that the only presence of P-gp at BBB level as normally described, is not enough to produce the impairment of AEDs entrance in the brain for the responders groups, and indicates that a functional P-gp up-regulation and other mechanisms must be present for explain the refractory phenotype

After the initial descriptions of the potential association between P-gp over-expression in the brain and refractory epilepsy by Tishler et al. (7) and Lazarowski et al. (8), several other groups have reported high levels of P-gp and MRPs expression in epileptogenic brain specimens from patients with refractory epilepsy (RE) (9-13). In these studies, P-gp was highly expressed not only in vascular endothelial cells but also in brain parenchymal cells. However it is still unclear whether this over-expression of efflux transporters is constitutive and exists before the onset of epilepsy or is a consequence of epileptic seizures, or drug treatments, or both, or perhaps, its overexpression is induced by the convulsive stress. With the exception of few clinical and experimental studies from our group and other researchers described below, the presence and potential role of P-gp in neurons from epileptic brain is not clearly established.

The abnormal parenchymal cells presents in the epileptogenic tissues from RE of different origins such as dysembryoplastic neuroepithelial tumors, focal cortical dysplasias and hippocampal sclerosis, express P-gp or MRP1, but it is not known if these P-gp or MRP1 positive parenchymal cells are also epileptogenic cells. However Sisodiya et al have suggested that in these cells express P-gp or MRP1 in a constitutive manner (12). Recently, we detected immunohistochemically, P-gp and MRP1 in abnormal balloon cells and dysplastic neurons, as well as in normal parenchymal cells presents in brain lesions from the epileptogenic cortical tubers but not at normal brain areas (14).

The presence of P-gp and MRP1 in abnormal cells of TS such as balloon cells and dysplastic neurons strongly suggests that the presence of these transporters can results from a constitutive expression of their respective genes. However, the presence of P-gp and MRP1 proteins observed in non-atypical cells (astrocytes, glial cells and vessels) from the same CT lesions, is more in favor with an inducible expression of the proteins. In the same brain specimens, new transporters were studied in theses same cases, and we found the expression of BCRP in BBB only, and MVP/LRP in several but not all ballooned cells (15). Similar results were recently published on adultas patients with RE (16)

The hypothesis of an inducible mechanism was demonstrated in experimental epilepsy model of our group (see below), and supported by most recent clinical data from Sisodiya et al. (17), who studied P-gp and MRP1 expression in brain specimen from a fatal case of human staus epilepticus. A net up-regulation of both transporters in the hemisphere with cortical dysplasia was found. Additionally, there was also a widespread up-regulation of both transporters in glia from the normal hemisphere. These results reinforce the idea that seizures can induce the expression MDR transporters.

In our clinical studies, we have been observed that Refractory Epilepsy could be related with other transporters than P-gp, because one case with transmantel cortical dysplasia and RE, P-gp was not detected in the brain lesion, but BCRP was highly

expressed in the dysplastic and ballooned neurons, and in the vascular endothelial cells of BBB. This particular location of BCRP in brain parenchyma cells suggest a potential role for BCRP in the refractory phenotipe of this case. The patient, remains asymptomatic after the surgical treatment (18). In other more recently studied case of satuts epilepsticus, with cortical dysplasia and refractory epilepsy, BCRP was observed in abnormal neurons and we failed to produce pharmacological coma (19).

Whether over- expression of the P-gp and MRP are demonstrated to be also a consequence of the seizure-induced stress, this concept will give a rational support to the criteria that "the repetitive uncontrolled seizures are a high risk factor to develop refractory epilepsy.

Persistent sub-therapeutic AEDs blood levels and MDR-1 gene over-expression in brain.

Refractory epilepsy is described in patients whom have adequate therapeutic levels of AEDs, without control of seizures; however, in some cases, patients have persistent low plasmatic levels of AEDs, despite their scrupulous compliance with the prescribed drug regimen. Often, laboratory's professional and physicians have no rational answer to this particular cases and non-detectable errors for AEDs measurement procedures methods are assumed. The persistent low plasmatic levels of AEDs, in spite of adequate drug administration and their relationship with the expression of P-gp in patients with refractory epilepsy was reported for the first time by Lazarowski A. et al. (8).

The patient presented seizures that failed to abate despite aggressive treatment with several combined AED regimes and evolved into several episodes of partial status epilepticus. Because of the failure of several AEDs, the patient was given nine loading doses of PHT (15-18 mg/kg) and lorazepam (0,1 mg/kg) intraveneously. In this context, therapeutic levels of phenytoin in blood and CSF can be achieved independently of the route of administration, as long as conventional loading doses are used, and in the case of phenytoin i.v. administration, 2 hours are enough to reach steady state concentrations within the therapeutic range.

However, in this case, phenytoin blood levels were invariably sub-therapeutic and ranged from 0.45 to 3.55 microg/mL, despite intravenous administration of several consecutive loading doses. Because, the seizures remained uncontrolled, surgical treatment, with total resection of the lesion was performed. Immunohistochemical analysis of the rejected tissues revealed high levels of MDR1 gene expression.

Another pediatric case of refractory epilepsy with persistent sub-therapeutic plasmatic values of AEDs and high expression of P-gp in brain was reported by our groupe. Among other therapeutic schedules the patient received phenytoin, carbamazepine and valproic acid in ususal doses. All these drugs failed to control seizures. Blood levels were monitored during a month by fluorescence polarization immunoassay. Finally, patient developed focal status epilepticus unresponsive to AEDs and was underwent surgical treatment with a significant improvement in its epileptic symptomatology. P-gp was present in astrocytes, neurons and significantly increased in VEC. Blood samples were collected daily for 25 consecutive days, prior to surgery, for measurements of phenytoin (PTH), carbamazepin (CBZ) and valproic acid (VA) trough

plasma levels. Blood levels were sub-therapeutic in 33% and 38% of samples for CBZ and PHT respectively. In the case of VA, 100% of samples had sub-therapeutic values (20).

Over-expression of P-gp in the brain do not explain the inappropriate blood levels of AEDs described in these cases but the results might indicate that, at least in these cases, P-gp over-expression could be a more general phenomenon that results in the accelerated clearance of AEDs not only from the epileptic lesions but also from the blood and peripheral tissues, perhaps in concert with other active metabolic and excretory mechanisms. Brain and systemic P-gp over-expression should be considered as a potential additional mechanism responsible for drug resistance to epilepsy treatment and highly suspected in patients with persistent sub-therapeutic drug plasma levels in their laboratory controls.

^{99m}Tc-MIBI-liver clearance: a kinetic marker in patients with RE.

Most drug metabolizing enzymes produce either covalent modifications of functional groups or conjugation of xenobiotic substrates with endogenous co-substrates to facilitate drug metabolism and excretion. The abundant expression of P-gp in tissues where drug alteration takes place suggests that P-gp plays central role facilitating drug elimination or their metabolites.

Bile flow plays important functions during drug metabolism. A large number of endogenous “waste products” and xenobiotic are secreted into the bile, often following oxidative or conjugative metabolism by hepatic detoxifying systems. Most canalicular transport elements involved in bile formation are members of the ABC transporter super-family, among them the glycoprotein P-gp and other recently discovered ATP-dependent organic anion transporters, the multidrug resistance-associated proteins (MRPs).

^{99m}Tc-hexakis-2-methoxyisobutylisonitrile (^{99m}Tc-MIBI) is used as a myocardial perfusion imaging agent. However, ^{99m}Tc-MIBI has been reported to be a transport substrate for P-gp as not metabolized compound and it is used for in vivo functional detection of P-gp in deferent tumors. In the upper image normal distribution of ^{99m}Tc-MIBI, correlates with the active efflux mediated by P-gp in excretory organs. The individuals with higher excretory function of drugs could be porters of high expression of active P-gp, according with recently description of polymorfisms in MDR-1 gene. An increased ^{99m}Tc-MIBI liver clearance was observed in pharmacoresistant epileptic patients, and five of these RE patients surgically treated, had high brain expression of P-gp (21)

Multidrug resistance gene (mdr-1) in experimental epilepsy models.

Several groups have demonstrated in different epileptic models, such as a single dose of intra-cerebroventricular kainate, chronic epilepsy, and status induced, a P-gp expression on BBB and brain parenchyma cells as astrocytes and neurons (22-24)

Kwan et al. (25) have demonstrated high brain expression of mdr-1 gene in genetically epilepsy-prone rats, after single audiogenic stimulation, suggesting that the P-gp expression is increased along with the seizure axis and the short-term audiogenic stimulation can induce the expression of mRNA mdr-1 transcripts for periods as long as seven days.

In a rat model of daily induction of seizures with 3-mercaptopropionic acid (MP), resulting in increased high expression of P-gp from VEC and adjacent astrocytes at day 4, to highly expression in neuronas at day 7 (26). We also have studied the effect of phenytoin (PHT) (30mg/kg) administration during 13 days to each previous MP doses, and observed that PHT protected from seizures MP-induced for the initial 3 days. After 4 days, the protective effect of PHT was speedy declined to disappear after 7 days of MP treatment indicating that MP administration during consecutive days, rats became refractory to PHT treatment, according with the increased expression of P-gp. (27) All results observed in these experiments indicated that mdr-1 over-expression depends on the seizure-stress frequency and exhibits a selective sequential enrollment of different type cells affected as endothelial cells, astrocytes and surrounding neurons that became mdr-1 positive after seizures, suggesting that the expression of P-gp in previously non-expressing cells, is a progressive process of selective cellular induction depending on intensity and time-constancy of seizure-injury. This observations are in agreement with the potential develop of "P-gp-positive seizure-axis" as proposed by Kwan and Brodie.

In this context it is worth noting that in a recent prospective study with 525 epileptic patients, it was shown that the development of RE directly correlated with the number and frequency of epileptic crisis before initiation of drug therapy (6).

More recently experiments of our group, demonstrated, that this model is refractory to phenytoin treatment, however, the additional administration of nimodipine (2mg/kg, ip) clearly reverts the refractory phenotype (27).

It was demonstrated that alterations in ion-exchange processes found in multiple drug resistance phenotypes, are related with Na^+ and Cl^- membrane transport and are responsible of the modifications of the intracellular pH and the membrane potential $\Delta\psi_0$. A significant and stable membrane depolarization occurs in MDR1-expressed cells. Relatively to sensitive cells, these resistant cells exhibit significant low membrane potential ($\Delta\psi_0$= -10 to –20) compared to normal physiological $\Delta\psi_0$ of –60 mV. These changes may lead to a reduced membrane binding of the drug (by 30% for example in case of a drug with a coefficient of partition equal to 1000) (28).

In case of cells over-expressing P-gp in epileptogenic tissues, and considering the fact that these cells may exhibit low membrane potential, this will lead to a persistent reduced threshold to stimuli by these cells, which then became more sensitive to new seizures.

The presence of P-gp at the surface of neurons could induce changes in their electrical membrane potential and consequently provoke changes in the expression/activity of AEDs target proteins. These alterations may be responsible of "non-responsiveness" to AEDs, resulting in refractory phenotype without any involvement of drug extrusion process. This will assume that patients with refractory epilepsy will be non-responsive to many AEDs even those that are non-P-gp substrates. This is in accordance with the clinical observations available to date indicating that patients are often resistant to multiple drugs and in some cases to all commonly used drugs, making surgery the only available treatment for them.

Conclusions.

The ABC transporters as MDR-1, MRP-1 and BCRP, are related with the epileptic refractory phenotype, and the understanding of their molecular properties can give to us, new tool for better selection of more effective therapeutic strategies, and avoid the invasive surgical treatments for Refractory Epilepsy.

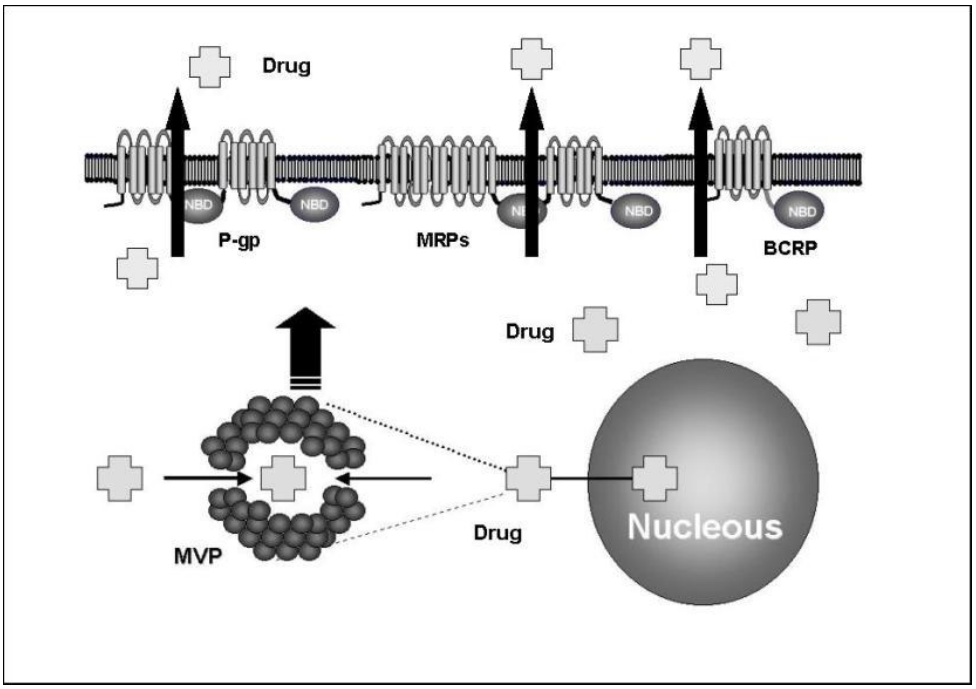

***Figure 1**. ABC transporters (P-gp, MRP and BCRP), and MVP, playing a drug efflux role.*

***Figure 2**. P-gp expression in cortical neurons from our PHT refractory epileptic model.*

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XXII CONGRESO LATINOAMERICANO Y 1ER IBERO-AMERICANO DE CIENCIAS FISIOLÓGICAS

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Buenos Aires, 4 al 7 de noviembre de 2006

Este año tendrá lugar en Buenos Aires el XXII Congreso de la Asociación Latinoamericana de Ciencias Fisiológicas (ALACF). Esta reunión congregará a científicos originarios de América Latina trabajando en sus países de origen, en Estados Unidos, en Europa y alrededor del mundo. Fisiólogos no latinoamericanos de primer nivel son también regularmente invitados. Esta vez la Sociedad Española de Ciencias Fisiológicas se asocia al evento, dándole especial interés y relevancia.

El objetivo central del Congreso es dar, a los fisiólogos trabajando y viviendo en Latinoamérica, la posibilidad de entrar en contacto con referentes en su campo de trabajo. Esto será especialmente cierto esta vez para aquellos radicados en el Cono Sur del continente (Bolivia, Brasil, Chile, Paraguay, Uruguay y Argentina).

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