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Short communication

Upregulation of breast cancer resistance protein and major vault protein in drug resistant epilepsy

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ABSTRACT

Purpose: Identifying factors involved in the development of drug resistant epilepsy (DRE) remains a challenge. Candidate gene studies have shown modulation of resistance to drugs by various multidrug resistance proteins in DRE. However the resistance to drugs in DRE could be more complex and multifactorial involving molecules in different pharmacokinetic processes. In this study for the first time we have analyzed the relative expression of four molecules with different drug resistance mechanisms in two most common DRE pathologies, mesial temporal lobe epilepsy (MTLE) and focal cortical dysplasia (FCD) with respect to each other and also with different non-epileptic controls.
Methods: Brain tissues resected from MTLE (n = 16) and FCD type I and II (n = 12) patients who had undergone surgery were analysed for mRNA levels of multidrug resistance-associated protein 1(*MRP1*), major vault protein (*MVP*), breast cancer resistance protein (*BCRP*), and one drug metabolising enzyme (*UGT1A4*) as compared to non-epileptic controls which were tissues resected from tumor periphery (n = 6) and autopsy tissues (n = 4) by quantitative PCR.
Results: We found significant upregulation of *MVP* and *BCRP* whereas *MRP1* and *UGT1A4* were unaltered in both pathologies. While upregulation of *BCRP* was significantly higher in MTLE (9.34 ± 0.45; $p < 0.05$), upregulation of *MVP* was significantly higher in FCD (2.94 ± 0.65; $p < 0.01$).
Conclusion: We propose that upregulation of *BCRP* and *MVP* is associated with MTLE and FCD and these molecules not only may have the potential to predict pathology specific phenotypes but may also have therapeutic potential as adjunct treatment in these pathologies.

1. Introduction

Despite the availability of new antiepileptic drugs (AEDs), ~20%–30% of people with epilepsy will not be seizure free and are said to have drug resistant epilepsy (DRE) [1]. DRE imposes serious threats to a patient's life including neuropsychological illness, psychiatric and social impairment, reduced marriage rates and decreased lifespan [2]. It is these patients who require a great deal of time and effort for effective treatment. There is also an economic burden on these patients with epilepsies (PWE) [2]. For better management of DRE, it is crucial to understand the exact pathogenesis of this neurological disorder. DRE is likely to be a multifactorial process including genetic factors, disease-related factors and factors resultant from treatment with AEDs [1,3]. There are several reports showing associations between many genetic variations and clinical drug resistance; however these associations are conflicting and are not equivocally replicated [4–6]. Several mechanisms of drug resistance have been proposed such as dysregulation of multidrug transporters (MDTs), reduced drug-target sensitivity, increased neuronal apoptosis, cytoskeletal alterations and reorganization of neuronal networks but the exact mechanism underlying drug resistance remains an enigma [3,7,8]. Altered expression of transporters and metabolic enzymes in blood-brain barrier (BBB) as well as barrier leakage have been linked to AED resistance and seizure genesis, respectively [8].

Abbreviations: DRE, drug resistant epilepsy; PWE, patients with epilepsies; AEDs, anti-epileptic drugs; MTLE, mesial temporal lobe epilepsy; FCD, focal cortical dysplasia; BCRP, breast cancer resistance protein; MVP, major vault protein; MDT, smultidrug transporters; BBB, blood brain barrier; UGT1A4, UDP-glucuronosyl-transferase; qPCR, quantitative PCR.

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Various multidrug resistance proteins such as multidrug resistance gene-1 (MDR1), MRP2 and MRP5 have been shown to be over expressed in animal models of epilepsy as well as in brain tissue resected from DRE patients [9–13]. Prior investigations have shown involvement of MRP1, BCRP, MVP and UGT1A4 in drug resistance in various neurological diseases as well as in cancer yet very few reports are available on their contribution to DRE [13–16]. MRP1 is a specific organic anion transporter and can cause efflux of antitumor drugs and some AEDs namely phenobarbital, carbamazepine, phenytoin, sodium valproate [12]. MVP is a lung infection resistance-related protein and is shown to play role in the vesicular transport of several compounds. MVP is non-specific in nature as a transporter and may affect the response to AEDs, by changing the subcellular compartmentalization of drugs [14]. UGT1A4 gene encodes a UDP-glucuronosyltransferase, an enzyme of the glucuronidation pathway and is shown to metabolize AEDs [15]. UGT1A4 is induced by carbamazepine and phenytoin and inhibited by sodium valproate. Role of UGT1A4 has so far not been clearly validated in DRE. BCRP is an ATP-dependent drug efflux transporter with a wide range of substrates, such as antitumor and few AEDs like carbamazepine, oxcarbazepine [16]. Reports related to the contribution of BCRP in AED resistance are contradictory. Some studies found no upregulation of BCRP in human epileptogenic brain tissue and no evidence for BCRP mediated AED transport in vitro, but other studies reported upregulation of BCRP expression in the microvasculature of epileptogenic brain tumors and in chronic epilepsy animal models [13,14]. Alterations in the expression level of transporters in the brain tissues of DRE patients is clinically relevant and need not to be extrapolated, unlike animal models. In order to understand the molecular mechanisms associated with DRE and identify pathology specific alterations with diagnostic and therapeutic potentials, we conducted this study. We analysed the possible association of four molecules with different drug resistance mechanisms, *MRP1*, *MVP*, *UGT1A4* with equivocal and *BCRP* with previously published contradictory reports, in two common DRE pathologies, mesial temporal lobe epilepsy (MTLE) and focal cortical dysplasia (FCD).

2. Materials and Methods

2.1. Ethical Statement

This study was reviewed and approved by Institutional Ethics Committee (IEC), All India Institute of Medical Sciences, New Delhi, India and Institutional Human Ethics (IHE), National Brain Research Centre, Manesar, Haryana, India, before the study began.

2.2. Patients

Patients who were diagnosed with DRE due to MTLE and FCD (Type I and II) and underwent surgery were included in this study (Table 1). Patients with dual pathology were not included in this

Table 1
Clinical characteristics of Patients.

PATIENT NAME	AGE (Years)/SEX	PATHOLOGY/COD	AEDs
M1	18/M	MTLE	CBZ, CLN, VPA
M2	24/F	MTLE	CLO, LEV, OXC
M3	26/F	MTLE	CBZ, CLO, ZNS
M4	39/M	MTLE	CLO, LEV, PBT, PHT
M5	15/M	MTLE	CLO, PHT
M6	15/M	MTLE	LEV, VPA, LTG, ZNS, CLO
M7	37/F	MTLE	LTG, VPA, CLO
M8	11/F	MTLE	CBZ, CLO
M9	20/M	MTLE	CLO, VPA
M10	36/M	MTLE	CBZ, CLO, LCS, LEV
M11	9/M	MTLE	PHT, CBZ
M12	27/F	MTLE	LEV, CBZ
M13	6/M	MTLE	CLO, LEV, PHT, VPA, CLN
M14	22/M	MTLE	CBZ, CLO, TPR
M15	15/M	MTLE	CLO, LCS, LTG, LEV
M16	20/F	MTLE	CLO, LCS, LEV
F1	12/F	FCD Type Ia	CLO, PHT, LEV
F2	24/F	FCD Type Ia	CBZ, LEV, TPR
F3	2/M	FCD Type Ia	CLN, VPA, LEV, VBN, ZNS
F4	6/M	FCD Type Ib	VPA, CLO
F5	11/F	FCD Type Ib	CBZ, CLO, LEV
F6	19/M	FCD Type Ib	CLO, CLN, LTG, LEV, VPA
F7	12/M	FCD Type Ic	LTG, VPA, TPR
F8	15/M	FCD Type Ic	VPA, LEV
F9	13/M	FCD Type IIa	CBZ, CLO
F10	15/M	FCD Type IIa	OXC, CLO, LCS
F11	28/F	FCD Type IIb	CLO, LEV
F12	34/M	FCD Type IIb	CLO, PHT, VPA
C1	26/F	Temporal-occipital tumour	–
C2	34/F	Right medial frontal low grade glioma	–
C3	18/M	Right frontal low grade glioma	–
C4	26/F	Temporal-occipital tumour	–
C5	35/M	Right Temporopartial Glioma	–
C6	30/M	Choroid Glioma	–
A1	25/M	Pelvic Injury	–
A2	18/F	Pelvic and lower limb injury	–
A3	16/M	Abdominal injury	–
A4	18/M	Head and abdominal injury	–

COD- Cause of death, M- MTLE, F- FCD, C- Control, A- Autopsy, CBZ- Carbamazepine, CLO –Clobazam, CLN- Clonazepam, DZP- diazepam, LEV- Levetiracetam, LTG –Lamotrigine, LZP- Lorazepam, OXC- Oxcarbazepine, PBT- Phenobarbital, PHT- Phenytoin, TPR –Topiramate; VPA-Valproinic acid, LCS- Lacosamide, ZNS- Zonisamide, VBN-Vigabatrin.