

# Unleashing the potential of brain endothelial cells in epilepsy

Volume 3 Issue 2 - 2015

Beatrice Mihaela Radu,<sup>1,2</sup> Mihai Radu,<sup>1,3</sup><sup>1</sup>Department of Neurological and Movement Sciences, University of Verona, Italy<sup>2</sup>Department of Anatomy, Animal Physiology and Biophysics, University of Bucharest, Romania<sup>3</sup>Department of Life and Environmental Physics, Horia Hulubei National Institute of Physics and Nuclear Engineering, Romania**Correspondence:** Beatrice Mihaela Radu, University of Verona, Department of Neurological and Movement Sciences, Strada Le Grazie 8, Verona 37134, Italy, Tel 00-39-0458027561, Fax 00-39-0458027155, Email [beatricemihaela.radu@univr.it](mailto:beatricemihaela.radu@univr.it)**Received:** October 27, 2015 | **Published:** October 28, 2015

**Abbreviations:** AEDs: Antiepileptic Drugs, BBB: Blood Brain Barrier, SE: Status Epilepticus, MRPs: Multidrug Resistance-associated Proteins, NVU: Neurovascular Unit, P-gp: P-glycoprotein, TLE: Temporal Lobe Epilepsy

## Editorial

Epilepsy, in particular temporal lobe epilepsy (TLE), is a neurological condition characterized by hypersynchronous neuronal firing and hippocampal atrophy and sclerosis. Beside the neuronal alterations several vascular characteristics of epilepsy have been described in experimental and clinical epilepsy, such as vascular inflammation, blood brain barrier (BBB) damage, recruitment of inflammatory cells, leukocyte-endothelial adhesion changes, angiogenesis etc.<sup>1-5</sup> Most of these symptoms involve alterations at the level of brain vascular endothelium and as brain endothelium is first active component of the neurovascular unit (NVU), any vascular inflammation determines the activation and altered function of all the others NVU partners, including neurons, and contributes to the neuronal hyperexcitability. Presently, there is a wide variety of advanced *in vitro* and *in vivo* techniques enabling the analysis of the changes underwent by BBB/NVU in neurological diseases, including epilepsy, stroke, Alzheimer's disease, Parkinson's disease, multiple sclerosis, brain ischemia, chronic pain etc.<sup>6</sup>

The most important and difficult to overcome clinical feature of epilepsy is drug resistance in approximately 20-30% of the patients and recent studies have pointed out that drug transporters expressed in brain endothelial cells are dramatically affected and might contribute to the epileptic condition. To date, in endothelial cells from patients with refractory epilepsy was identified the upregulation of multidrug resistance transporters, such as *MDR1* (P-glycoprotein: P-gp), *cMRP/ MRP2*, and *MRP5*, but not *MRP3*, and of the gene encoding cisplatin resistance-associated protein (*hCRA-α*).<sup>7</sup> In brain endothelial cells derived from temporal lobe resections of refractory epilepsy patients were detected increased levels of cytochrome P450 (CYP) enzymes, in particular CYP3A4,<sup>8</sup> that were colocalized with MDR1 with whom share substrates and inducers. On the other, the functional role of phase II enzyme UGT1A4 that is present in temporal lobe resections of refractory epilepsy patients and metabolizes lamotrigine should be further clarified.<sup>9</sup>

Epilepsy is associated with glioma, but not with glioblastoma, and seizures are one of the first clinical signs for the presence of a brain tumor or patients with brain tumors develop seizures as secondary symptoms. A recent study of multiple resistance transporters expression in the resected brain tissues of patients with glioma and epilepsy indicated a better patient outcome when MRP1 and MRP3 had a lower expression and a positive association between frontal tumors and refractory epilepsy without any correlation between tumor location and multiple resistance transporters expression.<sup>10</sup>

Oppositely, *in vitro* permeability studies of antiepileptic drugs (AEDs; e.g. phenytoin, lamotrigine and carbamazepine) on immortalized human brain endothelial cells hCMEC/D3 and primary porcine brain endothelial cells showed that there is no P-gp mediated transport and concluded that P-gp is not contributing to the molecular mechanisms underlying the refractory epilepsy.<sup>11</sup> In another study on hCMEC/D3, P-gp functionality was increased by 100μM carbamazepine and inhibited by 300μM valproate, while the other AEDs, such as levetiracetam, phenobarbital, phenytoin, and topiramate did not had comparable effect on P-gp functionality to the cytostatic drugs.<sup>12</sup> As clinical data on P-gp expression changes in refractory epilepsy are contradictory with respect to the *in vitro* P-gp mediated permeability studies, it remains to be further clarified the role played by P-gp in refractory epilepsy.

A very important hallmark of seizure activity is the BBB damage, but not the white blood cells presence in parenchyma, as demonstrated both on resected epileptic brain tissue and on the pilocarpine induced model in rats.<sup>13</sup> Leukocyte-endothelium interactions and leukocyte recruitment in brain parenchyma are essential events in epileptogenesis and their role in the epileptogenic cascade was demonstrated on mice pilocarpine induced epilepsy model.<sup>1,3</sup> Moreover, chemokines control leukocyte migration in epilepsy.<sup>2</sup> In the pilocarpine model were evidenced changes in the vascular plasticity network including the decrease of the total length of hippocampal blood vessels without alterations in hippocampal blood volume or flow after *status epilepticus* (SE)<sup>14</sup> and increased angiogenesis in hippocampus.<sup>15</sup> Vascular network changes have been also reported in the hippocampus of TLE patients. After SE was also reported vasogenic edema formation in piriform cortex that is mediated by endothelial mechanisms such as transient receptor potential canonical channel 3 (TRPC3) activation,<sup>16</sup> and/or tumor necrosis factor- $\alpha$ / endothelin-1 pathway.<sup>17</sup>

Although, multiple experimental and clinical studies indicated efflux transporters as being interesting pharmacological targets in epilepsy, their ubiquitous expression, that's beside brain endothelial cells, includes other NVU parenchymal components, such as neurons, astrocytes or microglia, prevents the development of cell-specific drug therapies.<sup>18</sup> On the other hand, considering leukocyte-vascular interactions involved in epileptogenesis were developed approaches for genetically targeting or blocking with antibodies the P-selectin glycoprotein ligand-1 (PSGL-1) in the pilocarpine-induced model,<sup>1</sup> and seems to be a promising beginning for developing clinical trials. In conclusion, brain vascular endothelium deserves a greater attention for developing efficient anti-epileptic drugs that are not good anticonvulsants but efficient drugs for diminishing vascular inflammation. Therefore, brain endothelium would be the best site targeted drug therapy in refractory epilepsy and might prevent the early events in epileptogenesis.

## Acknowledgements

B M Radu has a PhD fellowship from the Italian Ministry of Research (MIUR).

## Conflicts of Interest

There is no financial interest or conflict of interest to be declared.

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