## 5. SUMMARY

Epilepsy is a common neurological disorder of the brain with various etiology affecting 1 - 2 % of the population. Epilepsy in general is characterized by epileptic seizures (with motoric or psychic manifestation) that are caused by attacks of uncontrolled excitation of neurons in the brain. Antiepileptic drugs reduce excitability of the neurons and block fast spread of paroxysmal discharges within the brain.

Pharmacoresistant (refractory) epilepsy occurs in about one third of cases overall. It is a serious clinical problem associated with exhausting psycho-sociological complaints and increased risk of patient death. Resistance in epilepsy has probably a multifactorial and drug-nonspecific origin. Patients with refractory epilepsy are resistant to most of antiepileptic drugs, even though these drugs act by different mechanisms. This argues against epilepsy-induced alterations in specific drug targets as a major cause of refractory epilepsy and supports the hypothesis that a nonspecific mechanism, such as decreased drug up-take into the brain, is involved.

Treatment with antiepileptic drugs is usually a long time process, which is often terminated when patient dies. Depending on type of antiepileptic drugs administered to organism, a lot of adverse effects such as sedation, confusion, ataxia, hepatotoxicity or teratogenicity can be expected.

During life of people suffering from epilepsy there is often a need to medicate common disorders by co-administered drugs. In many cases there is a high risk of drug-drug interaction between antiepileptic and co-administered drug. Interaction at the level of expression and activity of cytochrome P450 and efflux drug ABC transporters can be introduced into high or low concentration of antiepileptic drug in epileptogenic centers. High concentration of antiepileptic drug is often associated with more expressed manifestation of adverse affects of antiepileptic drug and low concentration can be the cause of epileptic seizures occurrence.

Recently, effort of molecular pharmacologists is aimed at description of molecular mechanisms of transcriptional regulation of genes encoding cytochrome P450 and efflux drug ABC transporters. Some studies showed that activation of nuclear receptors such as constitutive androstane receptor (CAR, NR1I3) and pregnane X receptor (PXR, SXR, NR1I2) can be one of the mechanisms involved in transcriptional regulation.

Broad-spectrum antiepileptic drug valproic acid is able to affect gene expression by mechanism of histone deacetylases (HDAC) inhibition. Based on so far published data we supposed that in many cases an undocumented and more selective mechanism has to be employed. We suggested interaction of valproic acid with CAR and PXR to be additional mechanism that affects expression of some genes.

This dissertation thesis concerns with:

- Interaction of selected antiepileptic drugs with efflux drug ABC transporters and role of studied ABC transporters in development of resistance against antiepileptic treatment.
- Interaction of valproic acid with constitutive androstane receptor (CAR) and pregnane X receptor (PXR) and effect of this interaction on *CYP3A4* and *MDR1* gene expression.

**Interaction of selected antiepileptic drugs with efflux drug ABC transporters; role of studied ABC transporters in development of resistance against antiepileptic treatment**

P-glycoprotein (P-gp) was the first efflux drug ABC transporter (ATP-binding cassette) discovered in endothelial cells of the blood brain barrier (BBB). Further efflux drug ABC transporters detected and localized in the BBB were MRP2 (multidrug resistance-associated protein 2) and BCRP (breast cancer resistance protein). Up-regulation of efflux drug ABC transporters in the BBB is considered to be, analogically to multidrug resistance of tumor against treatment with cytostatic drug, the cause of lower up-take of antiepileptic drugs to