Involvement of gasotransmitter systems in the brain response to seizure activity in animal models of epilepsy

In clinical condition, the temporal epilepsy manifests itself as spontaneous, repeated seizures leading to inflammatory changes and neuronal degeneration, which increase the of seizure incidence in the future. One of the best-known causes of the increasing susceptibility to seizure activities is the increase in the general excitability of the brain resulting from imbalance between excitatory and inhibitory neurotransmitters, mainly between the glutamatergic and GABA-ergic systems, according to the classical concepts of epilepsy.

However, this concept was significantly modified after subsequent discoveries of intercellular interactions *via* very small gaseous particles: nitric oxide, carbon monoxide and hydrogen sulfide. It became evident that they play significant roles in the functioning of many organs, including the brain. Unfortunately, compared with the wide range of information from research on the cardiovascular system, very little is known about roles of the gaseous messengers - gasotransmitters, in the brain. Moreover, it is surprising that the current knowledge about possible roles of the gasotransmitters in the genesis, development and destroying effects of epilepsy comes mostly from studies of phenomena accompanying the brain damage, such as inflammation, oxidative stress and neurodegeneration, which are also typical of epilepsy. However, such an indirect approach to the problem does not give scientific satisfaction and therefore became the source of inspiration for the present project.

For the project we propose investigations on Wistar rats using two commonly used and well established models of pilocarpine- and electroshock-induced seizures.

The aim of the planned research is to obtain an integrated spatio-temporal profile of reactive changes in the enzyme systems producing nitric oxide, hydrogen sulfide and carbon monoxide.

This general, multidimensional profile will contain information on seizure-induced changes in the levels of each of the three gasotransmitters in the peripheral blood and brain (biochemical measurements), changes in the expression of proteins of gasotransmitter-producing enzymes (Western blots), spatial distribution of the glial response and of the blood-brain barrier disruptions, localization of neurons and glial cells co-expressing the enzyme proteins and on the extent of neuronal degeneration (quantitative immunohistology).

Additionally, the significance of correlations between these phenomena and changes in the intensity of seizure behavior and with variations in the spectrum of the brain bioelectrical activity (remote EEG recording) will be investigated.

The obtained results will allow to answer the following questions:

1) Are the the profiles of changes following electroshock- or pilocarpine-induced seizures similar or different for some phenomena?
2) Do the gasotransmitter systems react in a mutually correlated manner, positively or negatively?
3) What are the correlations between the gasotrasmitter systems response and:
    a) the intensity of the glial and neuronal reactivity,
    b) the intensity of the seizure behavior,
    c) changes in the EEG spectra recorded before, during and after seizures.

The answers to these questions will characterize the interaction of gas transmission systems and the way in which they simultaneously influence the brain response to seizures in two experimental models. Since only a few publications on this topic have appeared so far, the results obtained will be important to our understanding of the role of gasotransmitters in epileptogenesis.