

The influence of a new hybrid compound derived from 2-(2,5-dioxopyrrolidin-1-yl) propanamide on hippocampal neuroprotection and neurogenesis in a mouse pilocarpine model of epilepsy

Seizures in some 30% to 40% of patients with epilepsy fail to respond to antiepileptic drugs or other treatments. Hippocampal neurogenesis is very important for proper learning and memory functions. Seizure attacks, by alterations of neurogenesis, may contribute to the progressive memory dysfunction. It is a very serious problem especially in the group of adolescent patients, where proper learning and memory functions are essential. Very important issue for patients suffering from epilepsy is to receive a medication that will be able to stop the process of epileptogenesis, protect neurons and develop no or minimal side effects (especially, learning and memory disturbances). Considering the treatment with two or more antiepileptic drugs (AEDs) it is of particular importance that the AEDs should be selected based on their high anticonvulsant properties, high level of neuroprotection and minimal side effects. There is no doubt that the best solution for patients with refractory epilepsy is to find one ideal antiepileptic drug preventing different types of seizures without producing side effects that adversely affect patients quality of life. Looking for the best combination of already known AEDs we decided to combine chemical fragments of three AEDs active in three different animal models of epilepsy: the MES test (lacosamide, LCM), PTZ test (ethosuximide, ETS), and 6 Hz seizures (levetiracetam LEV, LCM), hypothesizing that one hybrid molecule may yield substances effective in all aforementioned preclinical animal seizure models.

The aim of our study is the evaluation of the relationship between treatment with a new hybrid compound derived from 2-(2,5-dioxopyrrolidin-1-yl) propanamide C11, ethosuximide (ETS), levetiracetam (LEV), lacosamide (LCM) and hippocampal neurogenesis and neuroprotection in a mouse pilocarpine model of epilepsy (PILO). Additionally, we will *in vivo* measure the spatial learning and memory after C11, ETS, LEV and LCM in PILO and non-PILO mice. Moreover, *in vivo* imaging of neurogenesis with magnetic resonance imaging and spectroscopy (MRI) will be performed after C11, ETS, LEV and LCM treatment in PILO and non-PILO mouse brain.

Our investigations are going to be performed on adult PILO mice reflecting patients with temporal lobe epilepsy. Patients in this group seem to develop seizures very intensively, which except a huge mental charge is also very dangerous from neurogenesis point of view. Disturbed proliferation of neural cells includes a risk of learning and memory dysfunction, which for patients is very important. Basing on the results obtained from our previous studies, we establish that C11 will play a key role in the process of neurogenesis as well as neuroprotection. Achievement of the positive results (a proper neurogenesis and neuroprotection) certainly will be qualified for more advanced pre-clinical investigations, especially in the group of patients with temporal lobe epilepsy. Results from additional pilocarpine-free group of animals will allow for determining the level of neurogenesis after drugs administration.

Proposed project will enable a deep analysis of the influence of antiepileptic drugs and a new hybrid C11 on the process of neurogenesis. Moreover, it will allow for the estimation of the commitment of used AEDs in neuroprotection and simultaneously preserve cognitive functions of the hippocampus.