Alterations in functionality of the $GABA_A$-receptor in epilepsy

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The $GABA_A$-receptor plays an important role in epileptogenesis. An important question is to what extent alterations of the $GABA_A$-receptor contribute to pharmacoresistance to antiepileptic drugs, which occurs in 25% of all patients. In the present study changes in the functionality of the $GABA_A$-receptor were studied in the post-Status Epilepticus (post-SE) rat model, in which the SE was induced by *ip* injections of kainic acid (KA).
The pharmacokinetic/pharmacodynamic (PK/PD) correlation of midazolam (MDZ) was determined before and at 4 or 14 days after induction of SE. Following an infusion of 10 mg/kg body weight MDZ, bloodsamples were taken, and the cortical EEG was recorded. The concentration MDZ in the blood (PK) was measured using HPLC-UV and the increase in the power of the β-frequency of the EEG was used as a measure of the effect of MDZ.
Preliminary analysis of the results show that for some rats the maximal effect of MDZ at 4 or 14 days after SE is reduced as much as 80% compared to the control situation. However, large interindividual variability between the KA-treated rats is observed. This was studied further, using *ex vivo* studies on the brains of the rats. Immunostaining with the neuronal marker NeuN showed a positive correlation between the extent of neuronal loss in the hilus of the hippocampus and the difference in maximal effect of MDZ between the PK/PD experiments before and 14 days after induction of SE.
In conclusion, this study illustrates the feasibility of studying the functionality of the $GABA_A$-receptor using a PK/PD experiment with MDZ. Moreover, a correlation was observed with the results of *ex vivo* studies on the neuronal loss in the brains of the rats.

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