Mechanism of Action of Clonidine in the WAG / Rij Model of Absence Epilepsy Evaluated Based on a Data-Driven Computer Model

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OBJECTIVES

Computer simulations became important tools in epilepsy research. Mathematical models are regularly used to explain the often controversial results of in vivo experiments, to interpret data or to integrate partial information into a complex theoretical framework. Current understanding concerning seizure generation in absence epilepsy is largely based on computer models of the thalamo-cortical neuronal network.

The goal of this study was to investigate whether one of those models can be used to determine the mechanism of action of clonidine, an α2-adrenergic agonist, in absence epilepsy.

METHODS

In the present study we compared *in vivo* and *in silico* models of absence epilepsy in terms of in which extent the simulation can reproduce the results of laboratory experiments. The *in silico* model of absence epilepsy included in this study have already been successfully applied by others to investigate the effects of GABAergic compounds. The *in vivo* EEG data were obtained from WAG/Rij rats with symptoms of absence epilepsy.

Computer model of absence epilepsy

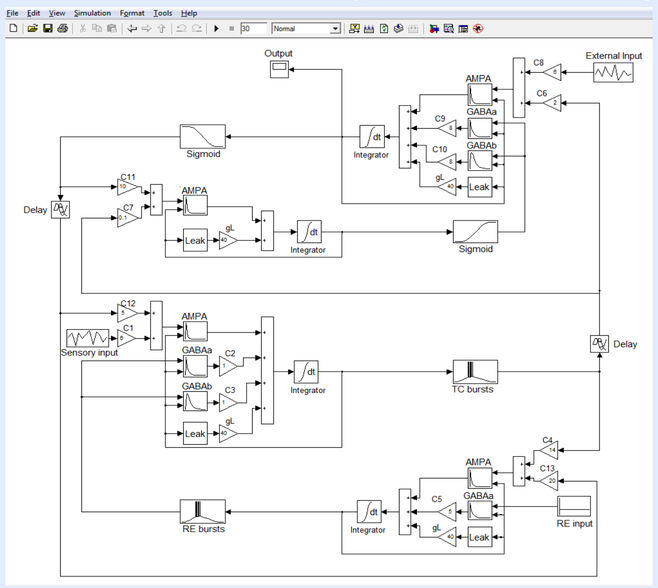

Figure 1. A Matlab simulink model was created to simulate the development of spike-wave discharges in absence epilepsy which included two celltypes of the thalamus and two celltypes of the cortex interconnected by glutamatergic and GABAergic connection

Bouwman, B. M., P. Suffczynski, et al. (2007). "GABAergic mechanisms in absence epilepsy: a computational model of absence epilepsy simulating spike and wave discharges after vigabatrin in WAG/Rij rats." Eur J Neurosci 25(9): 2783-2790.

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Kovacs Z, Czurko A, Kekesi KA, Juhasz G. (2010)." Clomipramine increases the incidence and duration of spike-wave discharges in freely moving WAG/Rij rats. " Epilepsy Res 90(1-2): 167-170.

Midzianovskaia, I. S., G. D. Kuznetsova, et al. (2001). "Electrophysiological and pharmacological characteristics of two types of spike-wave discharges in WAG/Rij rats." Brain Res 911(1): 62-70.

Sitnikova, E., A. E. Hramov, et al. (2009). "Sleep spindles and spike-wave discharges in EEG: Their generic features, similarities and distinctions disclosed with Fourier transform and continuous wavelet analysis." J Neurosci Methods 180(2): 304-316.

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RESULTS - CONCLUSIONS

The computer simulation reproduced the major characteristics of absence epileptic EEGs

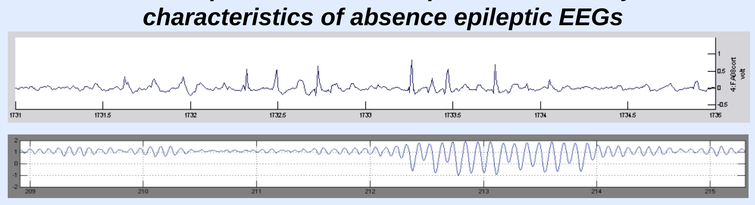

Figure 2. Top trace were recorded in vivo, bottom trace was simulated with the model. The frequency, duration of the seizures could be fitted to the in vivo data

We found that the number, duration and frequency of the seizures could be fit to the experimental data by systematical variation of the model parameters.

The effect of clonidine was modeled by varying I_T current amplitudes and GABA concentrations.

Decrease in the amplitude of the I_T current resulted in a decrease in the total length of seizures and duration of individual seizures whereas it caused an increase in seizure frequency. An increase in this parameter caused a rise both in the total duration and individual length of seizures, whereas the frequency decreased.

Effect of GABA concentration changes were examined in the thalamocortical population. After we enhanced GABA concentration we observed an increase in the total duration of spike-wave discharges while the SWD peak frequency decreased.

With systematic variation of the model parameters we successfully reproduced *in vivo* control measurements, but we were not able to completely reproduce the action of clonidine. Effect of clonidine caused increase in SWD number, total duration of SWD and SWD mean duration, whereas frequency decreased. In contrast I_T enhancement and modification of GABA concentration increased total duration of SWD and SWD mean duration, whereas frequency decreased, but this values are higher than *in vivo* clonidine-treated animals. In order to clarify the role of the noradrenergic system in absence epilepsy we have to include further details and mechanisms in the model.

	In silico model	*In vivo* controll	*In vivo* clonidine-treated
SWD number	35	22	134
SWD total duration (s)	112,78	168,81	887,55
SWD duration (mean, s)	3,22	7,67	6,62
Frequency (mean, Hz)	9,56	8,25	7,54

Table 1. The main variables of identified spike-wave discharges

Impact of the I_T current parameter change

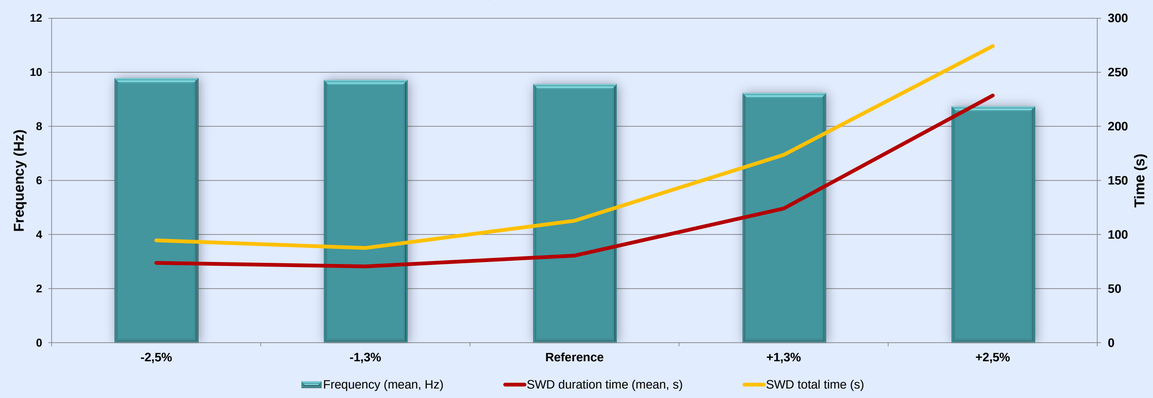

Figure 3. By increasing I_T current on the one hand the frequency decreased, on the other hand the SWD total time increased

Effect of the GABA concentration modification

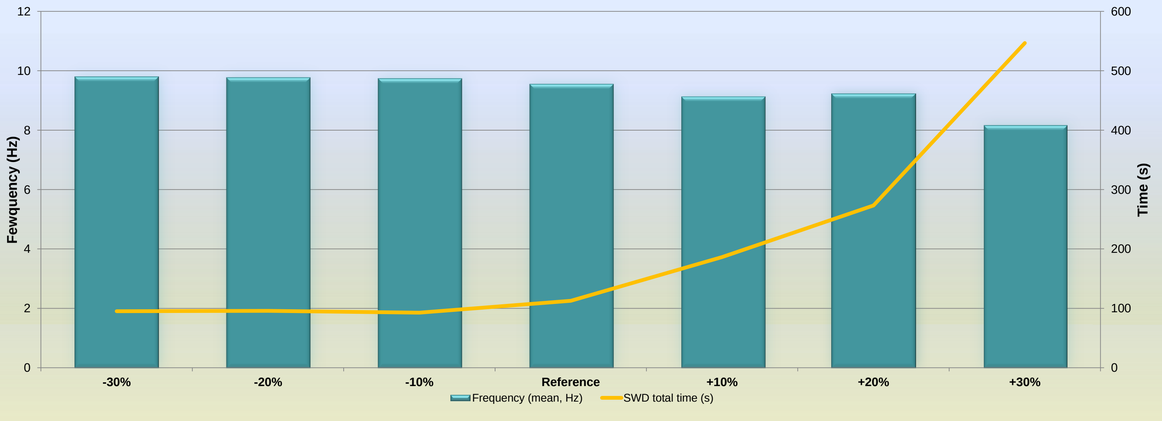

Figure 4. By increasing GABA concentration SWD total time increased significantly