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 thalamic-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.

RESULTS - CONCLUSIONS

The computer simulation reproduced the major characteristics of absence epileptic EEGs

We found that the number, duration and frequency of the seizures could be fit to the experimental data by systematic 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.

REFERENCES