GABAergic mechanisms in absence epilepsy: a computational model-rat comparison

Bouwman BM, Suffczynski P*, Van Rijn CM
NICI/Department of Biological Psychology, University of Nijmegen, Nijmegen, *Dutch Epilepsy Clinics Foundation Heemstede and Laboratory of Medical Physics, Institute of Experimental Physics, Warsaw University, Warsaw, Poland

In this study we analysed the influence of vigabatrin on spike and wave discharges (SWDs) in the EEG of WAG/Rij rats, an animal model for absence seizures and compared the in vivo data to a computational model (Suffczynski et al., in press) in which we studied the influence of modulating GABAergic neurotransmission in the thalamocortical loop.The parameter changes needed to obtain model behaviour similar to the in vivo SWD data were linked to the mechanism of action of vigabatrin. More specifically, the model output was used to predict whether the increase of GABAergic neurotransmission after vigabatrin is either homogeneous or heterogeneous throughout the brain.
In vivo, vigabatrin dose dependently increased the incidence of SWDs while it didn't affect the average duration of seizures. Also, the SWD peak frequency was decreased. In drug free (saline) conditions the distribution of SWD durations was well described by a gamma function while after application of 500 mg/kg of vigabatrin there was an exponential distribution. The distribution of the durations of the inter SWD periods was exponential in both conditions. These results suggest that SWDs in undrugged animals are terminated by a time-dependent process and that the termination of inter SWD epochs, which is equivalent to the onset of a SWD, occurs randomly in time. After vigabatrin, both the onset and offset of SWDs occur at random. Model simulations of manipulation with GABAergic neurotransmission in the whole network, or only part of the network, showed that the effects of vigabatrin are reproduced best by an relative increase of GABAergic neurotransmission at the level of the thalamic relay nucleus. We conclude that vigabatrin most likely affects inhomogeneously different parts of the thalamocortical circuitry. More specifically, we hypothesise that an increase of GABAergic neurotransmission by vigabatrin is most pronounced at the level of the thalamic relay nuclei.

B.M. Bouwman, University of Nijmegen, NICI/Department of Biological Psychology, P.O. Box 9104, 6500 HE Nijmegen, The Netherlands, t (+31) 024-3615566, e-mail b.bouwman@nici.kun.nl

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