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# THE EFFECTS OF VIGABATRIN ON THE BETA FREQUENCY SPECTRAL POWER IN THE EEG OF RATS DURING SLEEP AND ACTIVE BEHAVIOUR

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## Introduction

Characteristic features in the spectral content of the EEG are commonly used as biomarkers, i.e. specific effects of a drug on the EEG may be used to determine to which clinical drug class that drug will belong or what receptor mechanism underlies the effects. Several researchers (Cleton et al., 2000; Lopes da Silva, 2002; Visser et al., 2002) stated that the increase in the beta frequency spectral power can be used as a biomarker for a GABA agonistic mechanism of action. Vigabatrin is a GABAergic drug that enhances the concentration of endogenous GABA by inhibiting GABA-transaminase (Fraser, 1996; French, 1999). According to the biomarker hypothesis, vigabatrin must therefore also induce a power increase in the beta frequency range. However, all these reported biomarker effects of GABA agonists appear to have been measured during only one behavioural state, namely during active behaviour. Aim of the present study was to investigate the effects of vigabatrin on the beta frequency spectral power during both sleep and active behaviour.

## Methods

Male WAG/Rij rats were used (n=20, average weight= 340 grams). A cortical tripolar electrode was implanted during isoflurane anesthesia. The co-ordinates related to bregma were for the first frontal electrode A: 2.0, L: 3.5, for the second parietal electrode A: -6.0, L: 4.0 and the third was placed above the cerebellum. The rats entered the experiment three times and were randomized across the doses. The rats received three of the doses, either saline, 15, 31, 62, 125, 250 or 500 mg/kg vigabatrin i.p.. The time between the conditions was at least two weeks for each rat. The rats were allowed to move freely and at 6 hours following the vigabatrin injection EEG and behaviour were recorded during 30 minutes. Active behaviour was defined as: locomotion, rearing, digging and sniffing. Sleeping behaviour was defined as: immobile, curled up or lying straight with their eyes closed (Coenen et al., 1983; Tromp et al., 1990). Behaviour was scored independent of the EEG. The EEG signal was recorded between 1 and 100 Hz and sampled with 512 Hz. The power spectrum of the EEG was calculated, using a FFT procedure. The beta frequency range was defined as 13-29.75 Hz.

## Results

Figure 1 shows the spectral power in the beta frequency range during sleep and active behaviour as a function of vigabatrin dose. An ANOVA was performed with dose as a between-subject factor for each behavioural category.

There was a significant effect of vigabatrin on the power in the beta frequency range during active behaviour ( $F(6,89)=3.411$ ;  $p=.004$ ). Post-hoc analyses revealed a significant increase after 500 mg/kg vigabatrin compared to saline ( $p<.01$ ), 15 mg/kg vigabatrin ( $p<.05$ ), 31 mg/kg vigabatrin ( $p<.05$ ) and 125 mg/kg vigabatrin ( $p<.05$ ). To describe the dose-response relationship a sigmoid  $E_{max}$  model was fitted through the data ( $ED_{(2 \times \text{baseline})}=499$  mg/kg; S.E.= 49 mg/kg).

During sleep there was no significant overall drug effect on the power in the beta frequency range. However, a T-test revealed a significant decrease after 500 mg/kg vigabatrin compared to saline ( $p<.05$ ). To describe the dose-response relationship a sigmoid  $E_{max}$  model was fitted through the data ( $ED_{(0.5 \times \text{baseline})}=270$  mg/kg; S.E.= 54 mg/kg).

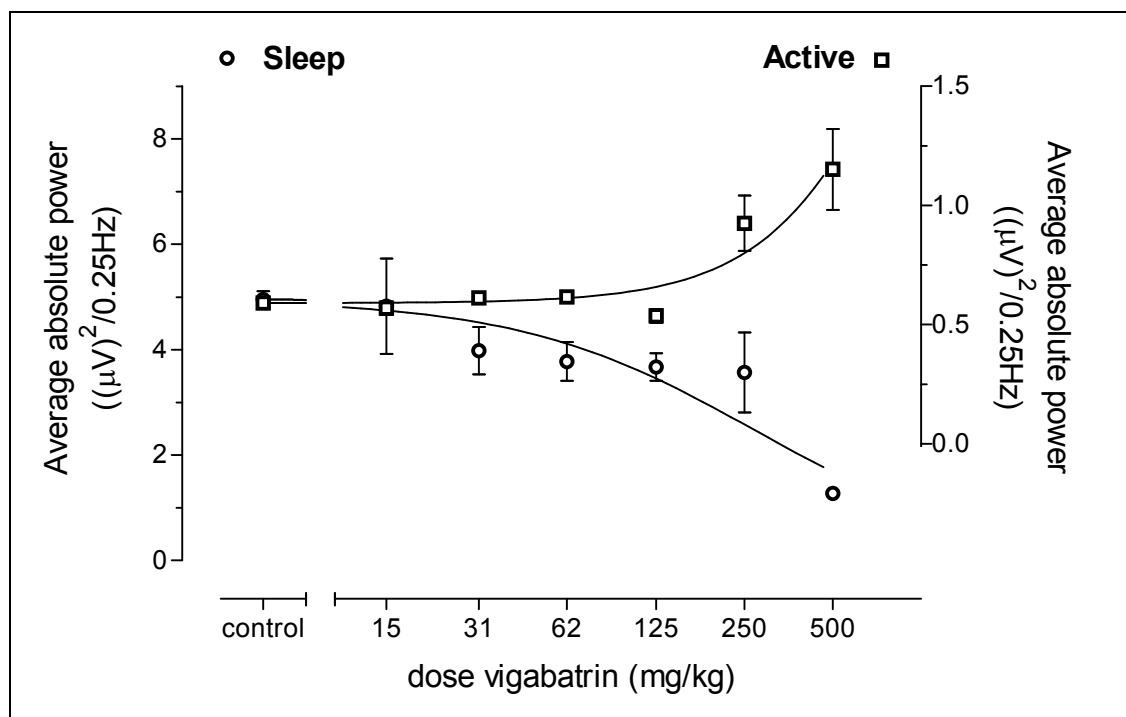


Figure 1. The spectral power in the beta frequency range during sleep and active behaviour as a function of vigabatrin dose.

## Discussion

As can be seen in figure 1, there is an increase of power in the beta frequency spectral power during active behaviour and a decrease during sleep (significant after 500 mg/kg). The increase of spectral power in the beta frequency range during active behaviour agrees with the literature in which an increase in the beta frequency spectral power has been used as a biomarker for GABA agonistic mechanisms of action. However, when looking at the beta frequency spectral power during sleep, it seems that this biomarker is not independent of behaviour.

Usually, after pharmacological manipulation with GABA agonistic drugs so called pharmacological dissociation, a dissociation of the normal relationship between behaviour and the EEG, is observed (Coenen & van Luijtelaar, 1991). However, both the increase of beta frequency spectral power during active behaviour and the decrease during sleep after (the highest dose of) vigabatrin show a strengthening of the normal relationship between behaviour and the EEG, in contrast to diazepam after which a behaviour independent beta increase is found (Bouwman et al., Unpublished results).

In conclusion we can state that whenever there is spoken of a biomarker effect, it should be made very clear during which behavioural state the measurements were obtained. Furthermore, vigabatrin seems to strengthen the normal relationship between behaviour and the EEG.

## References

1. Cleton, A., Altorf, B.A., Voskuyl, R.A. & Danhof, M. (2000). Pharmacokinetic-pharmacodynamic modeling of tiagabine CNS effect upon chronic treatment in rats: lack of change in concentration-EEG effect relationship. *European Journal of Pharmaceutical Sciences*, 12, 141-150
2. Coenen, A.M.L., van Hulzen, Z.J.M. & van Luijtelaar, E.L.J.M. (1983). Paradoxical sleep in the dark period of the rat: a dissociation between electrophysiological and behavioural characteristics. *Behavioral and Neural Biology*, 37, 350-356
3. Coenen, A.M.L. & van Luijtelaar, E.L.J.M. (1991). Pharmacological dissociation of EEG and behavior: a basic problem in sleep-wake classification. *Sleep*, 14, 464-465
4. Fraser, A.D. (1996). New drugs for the treatment of epilepsy. *Clinical Biochemistry*, 29, 97-110
5. French, J.A. (1999). Vigabatrin. *Epilepsia*, 40, s11-s16
6. Lopes da Silva, F. (2002). Pharmacology-EEG: from cellular to the network level. EEG $\beta$  spectral power as a biomarker for GABAergic inhibition and its role in the assessment of AEDs. *Methods and Findings in Experimental and Clinical Pharmacology*, 24 (suppl. D), 3
7. Tromp, J., Lahaije, M. & Nijssen, A. (1990). Sleep postures and power spectrum analysis of the EEG of the rat. *Behavioural Processes*, 22, 151-155
8. Visser, S.A.G., Wolters, F.L.C., Gubbens-Stibbe, J.M., Tukker, E., van der Graaf, P.H., Peletier, L.A. & Danhof, M. (2002). Mechanism-based pharmacokinetic/ pharmacodynamic modeling of the electroencephalogram effects of GABA-A receptor modulators: in vitro- in vivo correlations. *The journal of pharmacology and experimental therapeutics*, 304, 88-101