The anti-epileptic vigabatrin induces a behaviour-independent increase of delta- and a decrease of beta-power in the EEG of rats.

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INTRODUCTION

Vigabatrin and diazepam both are GABAergic drugs. Vigabatrin enhances the concentration of endogenous GABA by inhibiting GABA-transaminase, while diazepam enhances the efficacy of the endogenous GABA. As may be expected, the clinical effects of the two drugs overlap: e.g. both have anti-epileptic effects and both decrease the level of vigilance. The similarity of the effects on the EEG is however less clear. During slow-wave sleep, in drug-free rats, the EEG consists of high-voltage delta waves. Despite the induction of sleep, diazepam enhances the power of the high-frequency beta band. This phenomenon is called pharmacological dissociation. In contrast, vigabatrin slows down the EEG; the power in the delta and theta bands increases while that of the beta band decreases. However, although vigabatrin was observed to induce sleep, behavioural changes were not taken into consideration. Therefore, the rise in the power of the low frequency bands after vigabatrin may be caused by an increase in sleep. The aim of the present study was to investigate, in the rat, the effect of vigabatrin on behaviour and on behaviour-related EEG.

METHODS

Male Wistar rats were used (n=20, weights about 350 grams). A cortical tripolar electrode was implanted previously, coordinates related to bregma: one pole A-3.4, L 2.0, and two poles above the cerebellum. Each rat received both saline and vigabatrin 500 mg/kg i.p., separated by a 6-week interval. Using freely moving rats, both spontaneous behaviour and the EEG were recorded during 90 minutes, starting seven hours post-injection. The behaviour of the rats was categorised into four groups: 1) sleep: motionless with sleep-EEG, 2) passive wakefulness: passivity without a sleep-EEG, 3) automatic behaviour: eating, drinking and grooming, and 4) exploratory behaviour: sniffing, rearing and locomotion. The EEG signal was measured between 1 and 100 Hz and sampled with 512 Hz. The power spectrum of the EEG was calculated, using FFT, for each behavioural category. These spectra were divided in the frequency bands: delta: 1-4 Hz, theta: 5-8 Hz, alpha: 9-12 Hz, beta: 13-30 Hz, gamma: 31-60 Hz and a rest band: 61-100 Hz.

RESULTS AND DISCUSSION

Behaviour: See Figure 1. A two-way ANOVA with the within-subject factors drug (2) and behaviour (4) performed on the total duration of each behaviour, showed a significant effect for behaviour (F(3,15)=1198, p<0.001) and an interaction between drug and behaviour (F(3,15)=14.25, p<0.001). Post-hoc analyses with paired t-tests revealed that the duration of sleep during vigabatrin administration was significantly longer than during saline administration. There were no differences for passive wakefulness. The duration of automatic behaviour and of exploratory behaviour were significantly shorter for vigabatrin than for saline.

Spectral content of the EEG: See Figure 2. The first general frequency analysis of the EEG was without taking behaviour into account. An ANOVA with drug (2) and frequency band (6) as within-subject factors, showed a main effect of frequency band (F(5,15)=80.53, p<0.001) and an interaction effect (F(5,15)=8.93, p<0.001).

![Figure 1](https://example.com/figure1.png)
Post-hoc t-tests showed that the power of delta was significantly higher during vigabatrin administration compared to saline and the power in the beta- and rest band for vigabatrin was significantly lower than for saline. To explore whether the spectral changes could be ascribed to the increase in sleep, the spectra for each behavioural condition were calculated, see Figure 3. For exploratory behaviour, EEG data were very limited for vigabatrin. The other three behavioural categories were analysed separately using a two-way-ANOVA. During these three behavioural categories the effect of frequency band and the interaction between drug and frequency band were significant (F(5,13)>35, p<0.001, respectively F(5,13)>4.8, p<0.05). Post-hoc analysis showed that in all behavioural categories vigabatrin was associated with more power in the delta band and less power in the alpha and higher bands.

Indeed, vigabatrin was associated with more sleep\(^5\) (Figure 1) and higher delta power in the EEG\(^7\) compared to saline (Figure 2). It is shown that the power changes are observed in all behavioural states (Figure 3). Therefore, it is concluded that the increase in delta power cannot be ascribed to an increase in sleep but must be a genuine effect of vigabatrin or, more likely, is an effect of the enhancement of endogenous GABA. Furthermore, and in contrast to benzodiazepines, vigabatrin shows a decrease in beta activity. This decrease in beta power is independent of the behavioural state. Thus, in contrast to most anti-epileptics, vigabatrin is an anti-epileptic which shows an decrease in beta-power associated with an increase in delta-power.

REFERENCES

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