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EFFECTS OF R-BACLOFEN ON THE DELTA FREQUENCY BAND DURING ACTIVE AND PASSIVE BEHAVIOR IN RATS

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INTRODUCTION

GABA is the main inhibitory neurotransmitter of the CNS and activates two different receptor classes in the central nervous system: GABA_A and GABA_B receptors. It is well established that activation of GABA_A receptors favors sleep, which has led to the development of three generations of hypnotics. Besides GABA_A receptors also GABA_B receptors seem to be involved in the regulation of sleep (Lin et al., 1993, 1995; Gottesmann, 2002), suggesting a possible role of GABA_B agonists as hypnotics. Indeed, in humans the GABA_B agonist baclofen increases slow-wave sleep (Guilleminault and Flagg, 1984; Finnimore et al., 1995). Therefore, R-baclofen administration in rats is expected to increase the absolute power in the delta frequency band. To verify this, we studied the effects of R-baclofen on the average absolute power in the delta frequency band in WAG/Rij rats during both passive and active behavior.

METHODS

R-baclofen was dissolved in saline (0.9 %). The rats were injected intraperitoneally (i.p.) with saline (12.5 ml/kg) or with one of the following doses of R-baclofen: 0.65, 0.98, 1.48, 2.22, 3.33, 5.00 ml/kg (1ml/kg). Experiments were performed in adult male WAG/Rij rats (n=9 per dose, 6 months old). The rats were housed in Macrolon cages, and were maintained on a reversed 12-h light-dark cycle with lights on at 20.00 h. Food and water were available ad libitum. Isoflurane anesthesia was used during the implantation of a tripolar EEG electrode (Plastics One MS-332/2-A) on the cortical surface: one electrode in the frontal region (coordinates with skull surface flat and bregma zero-zero: A2.0, L3.5) and a second one in the parietal region (A-6.0, L4.0). The reference electrode was placed over the cerebellum. After surgery, the animals were allowed to recover for at least 2 weeks. On experimental days, 4 rats were placed in separate recording cages (19x19x40 cm) and connected with leads through swivels (to allow free movements) to an amplifier and a computer-based data acquisition system (Dataq Instruments, OH, USA). The EEG signals in a bandwidth between 1 and 100 Hz, were sampled with a frequency of 512 Hz. The EEG data (30 minutes after injection) during active (defined as walking, running and rearing) and passive behavior (defined as passive waking and sleep) were analyzed (in epochs of 2 s) using the Fast Fourier Transformation with a Hanning window (Brain Vision Analyzer Version 1.04.2002, Brain Products GmbH, München, Germany). The average absolute power in the delta frequency band (1-4.5 Hz) was calculated and analyzed using univariate analyses of variance in SPSS 11.5 for Windows (SPSS inc., Chicago, Illinois USA).

RESULTS

There was no effect of R-baclofen on the total spectral power in the EEG. Furthermore, besides effects on the delta frequency band, no consistent effects on other frequency bands were observed. Figure 1 shows the average absolute power in the delta frequency band during active behavior as a function of R-baclofen dose. There was a significant increase of the average absolute power in the delta frequency band during active behavior after R-baclofen ($F(6,56)=2.995$; $P=0.013$). To describe the dose-response relationship, a sigmoid E_{\max} model was fitted through the data ($ED_{(2x \text{ baseline})} = 3.94 \text{ mg/kg}$, $S.E. = 0.86 \text{ mg/kg}$).

Figure 1. The average absolute power in the delta frequency band as a function of R-baclofen dose during active behavior.

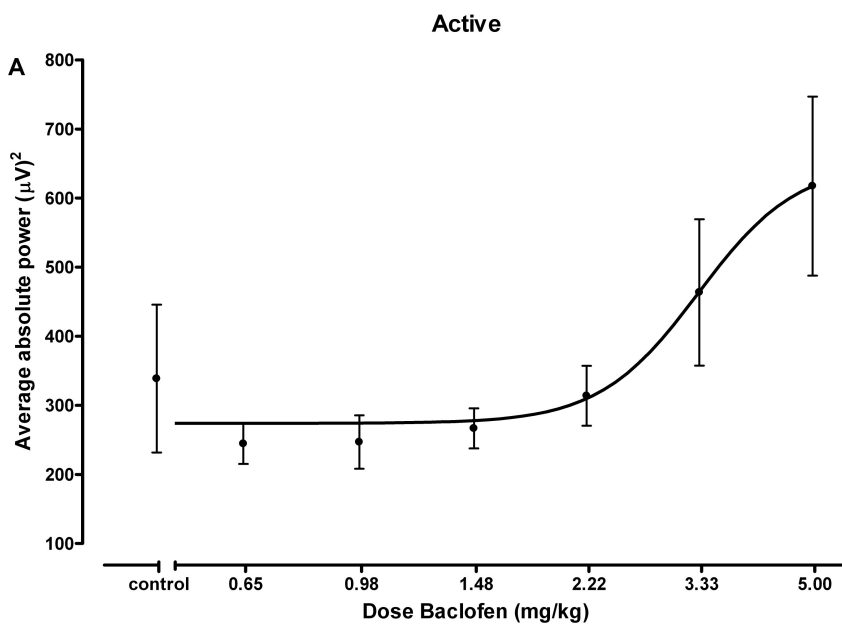
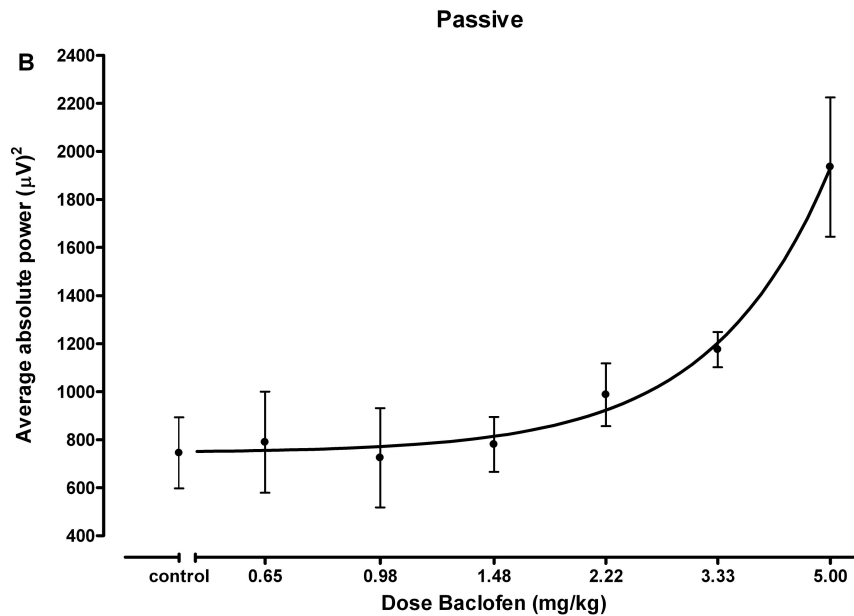


Figure 2 shows the average absolute power in the delta frequency band during passive behavior as a function of R-baclofen dose. There was a significant increase of the average absolute power in the delta frequency band during passive behavior after R-baclofen ($F(6,56)=5.806$; $P<0.001$). To describe the dose-response relationship, a sigmoid E_{\max} model was fitted through the data ($ED_{(2x \text{ baseline})} = 4.09 \text{ mg/kg}$, $S.E. = 0.24 \text{ mg/kg}$).

Figure 2. The average absolute power in the delta frequency band as a function of R-baclofen dose during passive behavior.



DISCUSSION

The increase in the average absolute power in the delta frequency band after R-baclofen agrees with an earlier report stating that administration of R-baclofen to GAERS (similar to WAG/Rij rats) produced a shift in spectral power away from the higher frequencies towards the delta band (Richards et al., 2000). Under normal physiological circumstances, a fairly good relationship exists between the behavior and EEG. For instance, delta frequency oscillations represent sleep or sleep-like states (Coenen and van Luijtelaar, 1991). However, in the present study the increase in the average absolute power in the delta frequency band is independent of behavior, such an effect is commonly called pharmacological dissociation (Coenen and van Luijtelaar, 1991). On the other hand, it might indicate that even during active behavior the R-baclofen treated rats are sleepier than controls as is suggested by the increase in the average absolute power in the delta frequency band. However, the nature or intensity of the active behaviors might have been altered by R-baclofen, which might be a confounding factor. Nevertheless, this would still support the suggestion that even during active behavior the R-baclofen treated rats might be more sleepier than controls. Thus, the data presented here suggest that R-baclofen and other selective GABA_B agonists might have hypnotic properties.

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