D13/289.27

Eminent Increase in EEG Gamma Oscillation in the Wistar Kyoto Rat Model of Treatment-Resistant Depression After Ketamine Treatment

S. Kantor[1], M. Duxon[1], N. Upton[1]
[1]Transpharmation LTD, London, United Kingdom

Transpharmation
Science that translates into results

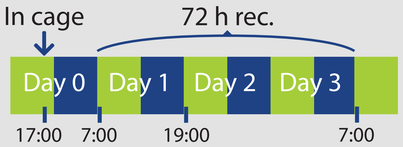
Introduction

Wistar–Kyoto (WKY) rats exhibit abnormal behavioural, hormonal, neurochemical as well as sleep-wake characteristics that are often associated with depression. Since WKY rats show decreased sensitivity to conventional monoamine-based antidepressant treatment, they are used as a model of treatment-resistant depression (TRD). The N-methyl-D-aspartate-receptor antagonist ketamine has emerged recently as a rapidly acting antidepressant with high efficacy in TRD patients. The aim of this study was to determine whether a subanaesthetic dose of ketamine has differential effects on sleep-wake behaviour and brain oscillations in WKY rats in comparison with Sprague-Dawley (SD) rats.

Methods

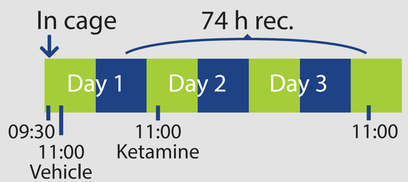
EEG surgery and recording

8 SD and 8 WKY adult (200-250 g) male rats were surgically implanted with telemetry transmitters for EMG and fronto-parietal EEG recording. Briefly, we placed a telemetry transmitter (F40-EET; DSI, USA) into the peritoneal cavity and the tip of EEG leads epidurally over the frontal (2 mm anterior / 1 mm lateral to Bregma) and parietal (0 mm anterior / 1.5 mm lateral to Lambda) cortices under isoflurane (2-5%) anesthesia. Then the animals were pair-housed and maintained in a room with controlled temperature (20-22°C) and a light-dark cycle (12h/12h, lights on: 7am) with food and water available ad libitum. Following post-surgical recovery, the rats were placed individually in recording boxes, and baseline sleep-wake behaviour was recorded for 72 h (see below). EEG/EMG signals were amplified, analogue filtered (1-50 Hz), digitized (256 Hz), digitally filtered (EEG: 1-50 Hz and EMG: 5-50 Hz), and then stored on a PC for offline analysis (Spike2; CED, UK).



Drug treatment

On test day, the rats were treated with vehicle, then 24 h later, with a single dose of ketamine (10 mg/kg, s.c.), and EEG, EMG, locomotor activity were recorded (see below).



Data Analysis and statistics

Data analysis comprised automatic sleep-wake scoring and power spectral analysis of the EEG. Vigilance states were automatically scored as wake, non-REM (NREM) sleep, or REM sleep in 10 second epochs using a customized algorithm (SleepSign, Kissei Comtec, Japan). EEG power spectral analysis was performed on the data recorded 4 h post-treatment. EEG power spectra were computed for consecutive 2 s epochs by fast Fourier transformation (Hanning window, 0.5 Hz resolution) between 1-50Hz. Epochs with artefacts (5xSTD of RMS) were discarded. Data were presented in 1 Hz bins, and the bins were marked by their upper limits. Repeated measures ANOVA followed by Tukey post-test was used to compare the different groups (GraphPad, Prism 8).

Results

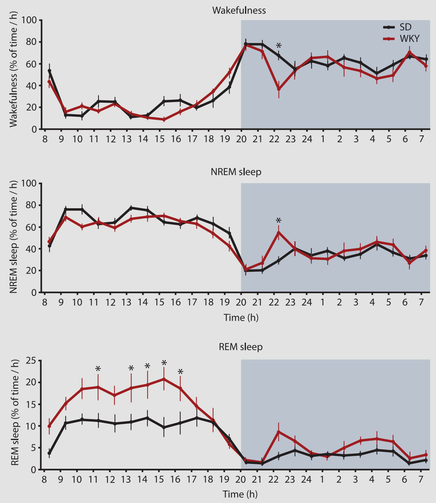


Figure 1. WKY rats spent almost twice as much time in REM sleep as SD rats during the light period. The diurnal pattern of wakefulness, non-REM (NREM) sleep, and REM sleep is shown in Sprague Dawley (SD) and Wistar Kyoto (WKY) rats after averaging three days of consecutively recorded data. The dark period is shown as shaded area. Data are

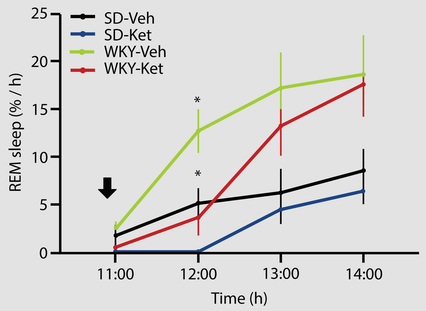


Figure 2. Acute treatment with the sub-anaesthetic dose of ketamine suppressed REM sleep in both SD and WKY rats. Changes in the percentage of REM sleep amount are shown in Sprague Dawley (SD) and Wistar Kyoto (WKY) rats after treatment (arrow) with vehicle (Veh, 2 ml/kg) or ketamine (Ket, 10 mg/kg, s.c.). Data are presented as mean ± SEM in 1 h intervals. *P < 0.05 vs vehicle treatment in the same strain (Tukey post-test).

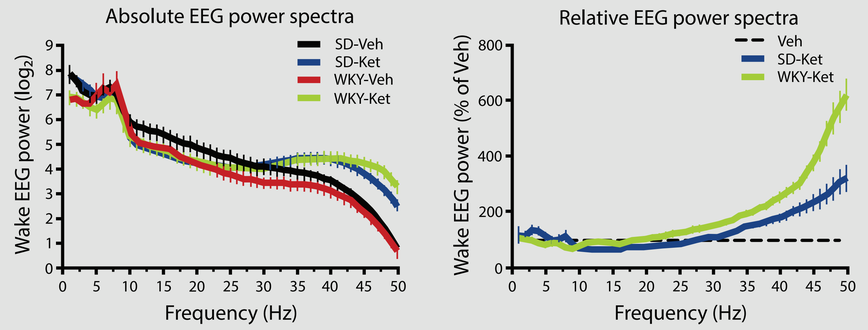


Figure 3. Acute ketamine treatment increased wake-EEG gamma power in both SD and WKY rats in the 1st hour post-treatment. Changes in absolute (left) and relative (right) power values of EEG spectra during wakefulness as shown in Sprague Dawley (SD) and Wistar Kyoto (WKY) rats in the first hour after treatment with vehicle (Veh, 2 ml/kg) or ketamine (Ket, 10 mg/kg, s.c.). The EEG power spectral values after ketamine treatment were normalized to the power spectral values of vehicle treatment (100%). Data are shown as mean ± SEM in 1 Hz bins.

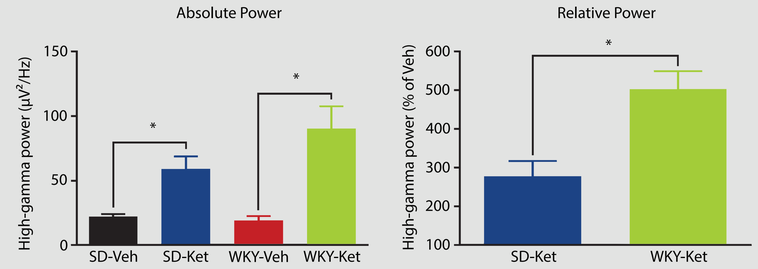


Figure 4. The increase in high-gamma power after ketamine treatment was almost twice as high as in WKY rats than in SD rats. Changes in the amount of wake-EEG high-gamma power (45–50 Hz) as shown in Sprague Dawley (SD) and Wistar Kyoto (WKY) rats in the first hour after treatment with vehicle (Veh, 2 ml/kg) or ketamine (Ket, 10 mg/kg, s.c.). The EEG power spectral values after ketamine treatment were normalized to the power spectral values of vehicle treatment (100%). Data are shown as mean ± SEM. *p < 0.05 vs vehicle treatment in the same strain (Sidak post-test).

Conclusions

- Ketamine is more effective in modulating cortical activity in the WKY rat model of depression than in control SD rats.
- An eminent increase in EEG gamma oscillation after treatment may indicate a therapeutic potential in depression, although this notion needs to be further investigated.
- Since the sleep and EEG abnormalities in WKY rats largely recapitulate the changes seen in TRD patients, these neurophysiological measures may serve as key translational tools in an effort to discover novel therapeutics against TRD.

Contact

www.transpharmation.co.uk
sandor.kantor@transpharmation.co.uk

NO – PHOTO / RECORD