Oxaliplatin-induced neuropathic pain is associated with poor sleep quality and reduced EEG alpha power in the rat

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INTRODUCTION

Platinum-based chemotherapeutics such as oxaliplatin are important tools in an oncologist's arsenal for treating patients with cancer.

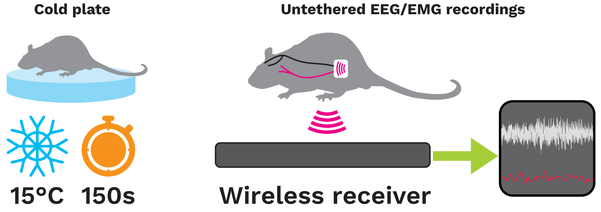
However, their use is limited because of serious side effects such as neurotoxicity that can lead to neuropathic pain, sleep disturbances, attention or memory deficits. These can often reduce patient compliance or affect treatment regimens if they become too impactful for the patient.

By understanding the pathophysiological changes induced by chemotherapeutic treatments and the side effects they cause may help in choosing the correct treatment strategies for patients with less side effects, leading to better patient compliance. Particularly for chemotherapy induced neuropathic pain for which electroencephalogram (EEG) recordings presents a potential objective and translatable marker.

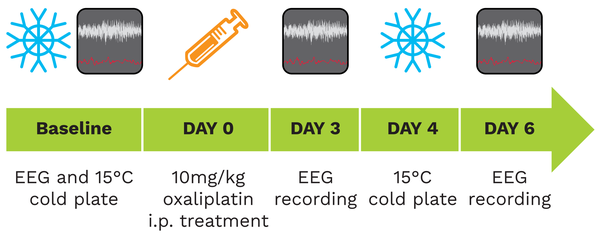
We hypothesized that oxaliplatin treatment would cause neuropathic pain, disrupt sleep and alter EEG oscillations in an animal model similar to the side effects seen in human patients.

METHODS

intraperitoneal wireless transmitters (HD-S02, DSI USA) and epidural EEG and electromyogram (EMG) electrodes. All animals were allowed to full recover after surgery before any testing commenced. Animals were maintained on a 12/12h light dark cycle and provided food and water ad libitum.



Neuropathic pain development of cold plate induced paw withdrawal threshold changes and EEG/EMG signals were measured.



EEG/EMG signals were amplified and filtered (EEG: 0.5-100 Hz and EMG: 5-100 Hz). Then EEG, EMG and locomotor activity (LMA) recordings were semi-automatically scored as wake, rapid eye movement (REM) sleep or non-REM (NREM) sleep in 10s epochs using SleepSign (Kissei Comtec, Matsumoto, Japan), and then visually inspected and corrected by a trained analyst blind to the treatment conditions.

All experiments were conducted under the authority of United Kingdom Animals (Scientific Procedures) Act 1986 and with the approval of Royal Veterinary Colleges' Animal Welfare and Ethical Review Body and in compliance with the ARRIVE guidelines.

RESULTS

Increased wake alpha / decreased NREM delta power

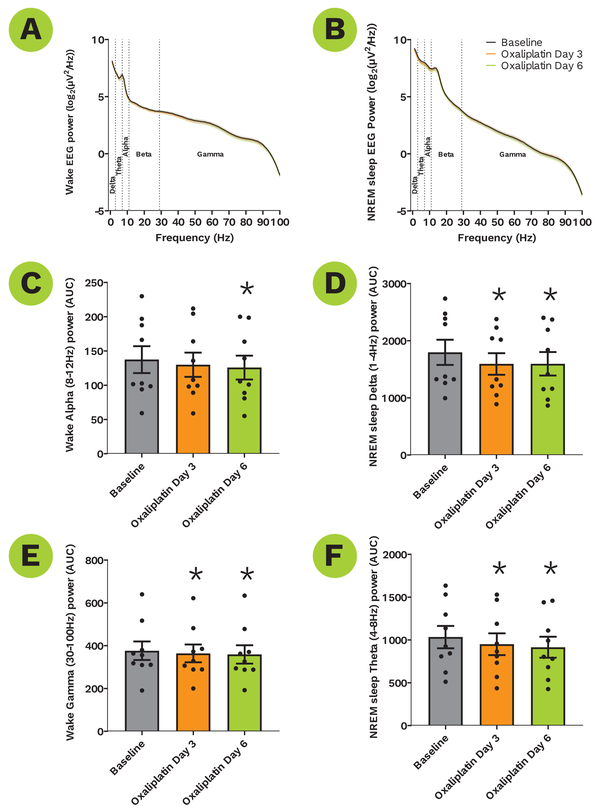


Figure 1: Oxaliplatin treatment decreased wake alpha and gamma power as well as decreases NREM sleep delta and theta power in the rats.
Changes in wake (A) and NREM sleep (B) EEG power spectra as well as in wake-EEG alpha (8-12Hz) and gamma (30-100Hz) power (C, E) and NREM sleep-EEG delta (1-4Hz) and theta (4-8Hz) power (D, F) are shown in the rats on day 3 and 6 after oxaliplatin (10 mg/kg, i.p.) treatment. Data are presented as mean ± SEM. *P < 0.05 vs baseline.

Statistical results

Figure 1: Repeated measures one-way ANOVA with Dunnett's post hoc test. C) $F(2,16) = 4.80$, $p = .023$, D) $F(2,16) = 8.50$, $p = .003$, E) $F(2,16) = 6.83$, $p = .007$, F) $F(2,16) = 27.1$, $p < .001$.

Figure 2: Repeated measures one-way ANOVA with Dunnett's post hoc test. A) $F(2,16) = 3.90$, $p = .042$, B) $F(2,16) = 0.81$, $p = .461$, C) $F(2,16) = 2.40$, $p = .122$, D) $F(2,16) = 2.92$, $p = .083$.

Figure 3: A) Paired two-tailed t-test $t(8) = 2.55$, $p = 0.034$, B) Pearson's correlation $r(8) = -0.381$, $p > .05$.

Fragmentation of sleep-wake behaviour

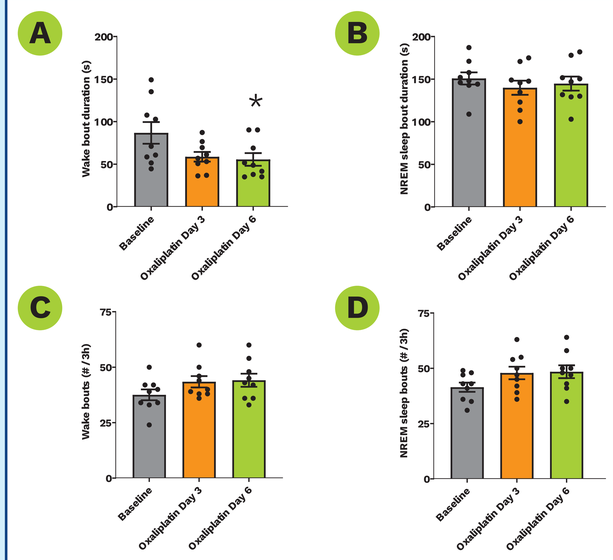
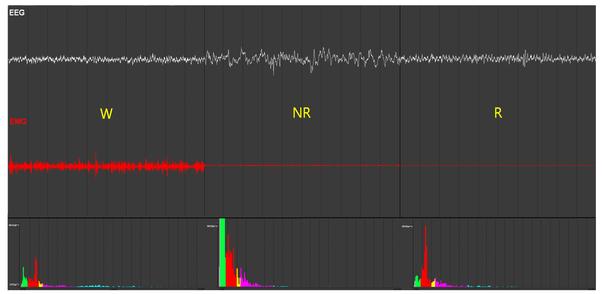


Figure 2: Oxaliplatin caused a fragmentated sleep-wake behavior in the rats as shown by the increase in the duration and decrease in the number of wake and NREM sleep bouts.
Changes in average duration (A, B) and total number (C, D) of wakefulness (A, C) and NREM sleep bouts (B, D) are shown in the rats during a three hour period starting after the animals were acclimatized to the recording environment. Data are presented as mean ± SEM. *P < 0.05 vs baseline.

Sleep-wake scoring



Representation of sleep-wake scoring of 10 second epochs using EEG and EMG data recorded along with individual epoch EEG power spectral data.

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Oxaliplatin induces neuropathic pain

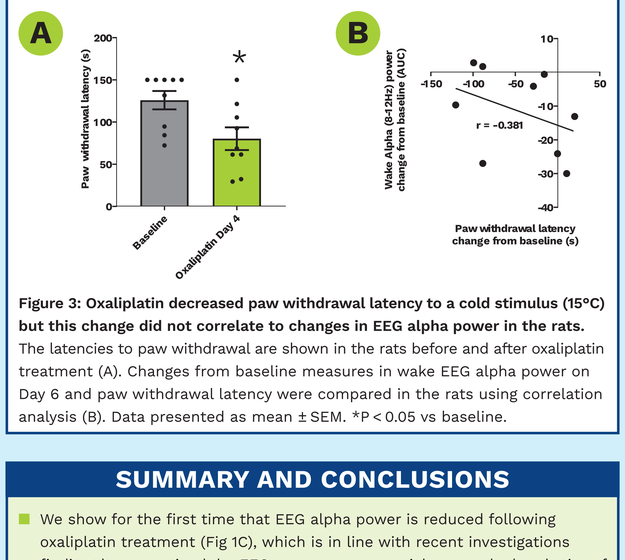


Figure 3: Oxaliplatin decreased paw withdrawal latency to a cold stimulus (15°C) but this change did not correlate to changes in EEG alpha power in the rats.
The latencies to paw withdrawal are shown in the rats before and after oxaliplatin treatment (A). Changes from baseline measures in wake EEG alpha power on Day 6 and paw withdrawal latency were compared in the rats using correlation analysis (B). Data presented as mean ± SEM. *P < 0.05 vs baseline.

SUMMARY AND CONCLUSIONS

- We show for the first time that EEG alpha power is reduced following oxaliplatin treatment (Fig 1C), which is in line with recent investigations finding decreases in alpha EEG power as a potential non evoked endpoint of neuropathic pain[1].
- A reduction in EEG gamma power (Fig 1E) could suggest impaired cognitive function such as attention because gamma oscillation are associated with many cognitive processes, which are often negatively affected in chemotherapy patients[2],[3].
- Oxaliplatin reduced sleep quality shown by decreased low frequency (delta and theta) EEG power (Fig 1D, F) and fragmented sleep-wake behaviour in the rats (Fig 2), which has also been seen in human oxaliplatin patients[4],[5].
- The changes in alpha power did not correlate to traditional evoked cold plate measures of neuropathic pain in this model (Fig 3).

Disrupted sleep, neuropathic pain and altered cognition have a large impact on a chemotherapy patient's wellbeing affecting their treatment, social and work life. We have demonstrated positive results of how these can be measured in a preclinical model, allowing future research to identify adjunctive treatments for oxaliplatin patients to improve their treatment regiment.

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