PTU62: Modulation of laser evoked potentials (LEPs) by lacosamide, pregabalin & tapentadol in awake rats

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Introduction & methods

- Current treatments for pain often provide incomplete symptom relief and are frequently accompanied by adverse effects and the potential for addiction.
- This study is part of a larger project (IMI-PainCare - BioPain subproject) profiling a range of translatable assays quantifying nociceptive system function in rodents and humans.
- Laser-Evoked Potentials (LEPs) are proposed as a quantitative translatable assay that can be utilized both preclinically and in humans that provides an objective assessment of nociception.
- Here we examine the basic properties of rodent LEPs and profile their modulation by standard-of-care compounds in awake, behaving rats.
- 12 adult male Wistar rats were implanted with multiple EEG (frontal, somatosensory, cingulate and occipital cortices) and depth electrodes (amygdala, prelimbic and insular cortices) to record resting-state and evoked activity (LEPs/auditory-evoked potentials (AEPs)).

Laser stimuli evoke graded behavioural responses in awake rats

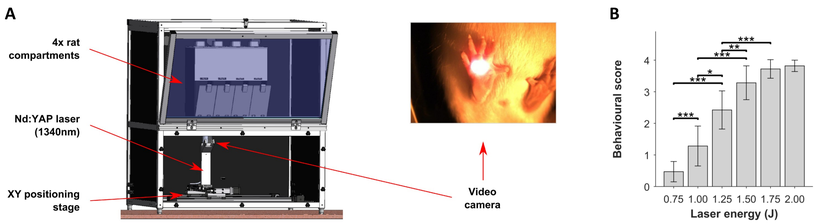

Figure 1. (A) Apparatus overview. Four individual rat compartments were located on a glass floor above a fibre optic cable which transmitted the light from an infra-red Nd:YAP laser allowing remote targeting of the laser to the plantar surface. (B) Distribution of mean behavioural scores (repeated measures ANOVA, Bonferroni correction for multiple comparisons, *p<0.05, **p<0.01, ***p<0.001).

Laser stimuli trigger LEPs in the rat brain

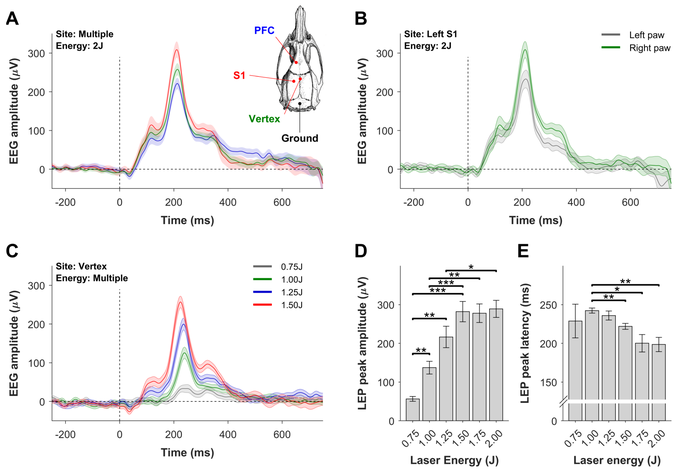

Figure 2. Form of the LEP with respect to EEG recording site (A) and side of laser stimulation (B). (C) Influence of laser energy on the LEP waveform at the vertex site. (D & E) Relationship between amplitude/latency of averaged vertex LEPs and laser energy, irrespective of behavioural response. Repeated-measures ANOVA, Bonferroni correction *p<0.05, **p<0.01, ***p<0.001.

Single-trial analysis identifies 'fast' and 'slow' classes of LEP responses.

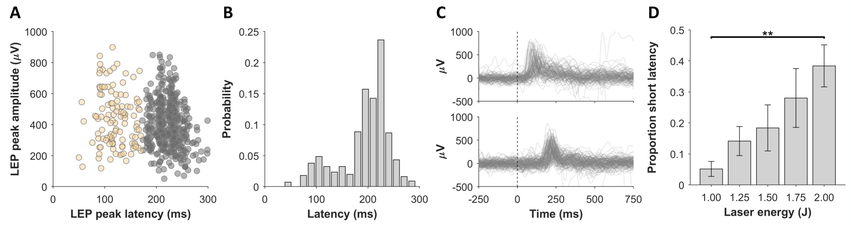

Figure 3. (A) LEPs at energies ≥1J and behavioural scores >0 can be split using k-means clustering to form two groups. (B) A bimodal distribution is apparent in the probability histogram of latencies reflecting the presence of responses with short and long latencies centred at ~120 and ~220ms (C) 150 randomly selected examples of raw LEPs identified as short (upper) or long (lower) latency. (D) The proportion of short latency events increases with increasing laser energies (repeated-measures Friedman test, Dunn's correction). ** p<0.01.

Intraplantar capsaicin preferentially blocks putative C-fibre mediated LEPs

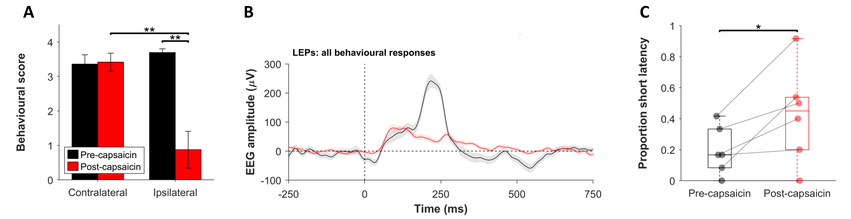

Figure 4. (A) Behavioural scores following 1.5J laser stimulation of the capsaicin-(ipsilateral) and untreated (contralateral) paws (repeated measures ANOVA with time and side as within subject factors, Bonferroni correction for repeated comparisons). (B) Mean raw LEPs pre- and post-capsaicin, with data pooled across all behavioural responses. (C) The proportion of short latency (peak latency < 0.172s) events showed a significant increase post-capsaicin (Lilliefors test for normality, paired t-test). *p<0.05; **p<0.01.

Pharmacological modulation of LEPs

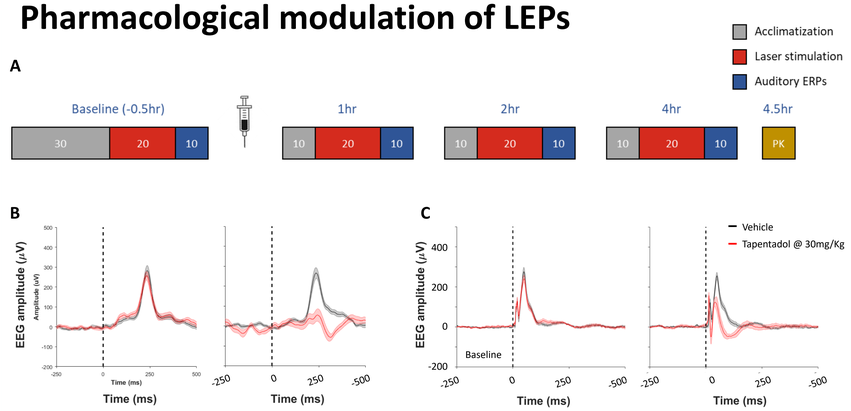

Figure 5. (A) Protocol for pharmacological studies testing 3 analgesic drugs. (B & C) 30mg/Kg tapentadol, but not vehicle reduces LEP (B) and AEP (C) amplitude relative to baseline.

Analgesics reduce LEP amplitude and behavioural responses

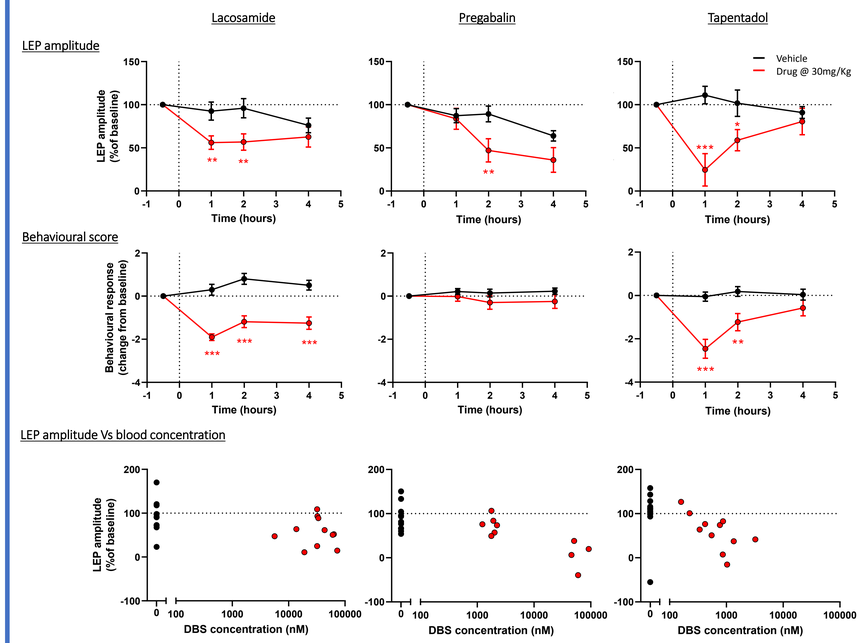

Figure 6. All analgesics tested reduce LEP amplitude with a time course compatible with their pharmacokinetic profile (data not shown). Similarly, their effects on concurrent behavioural responses follow a broadly similar time course. Correlations between the reduction in LEP amplitude (lacosamide@1hr, pregabalin@2hr, tapentadol@1hr) and blood concentration of each drug demonstrate the PK/PD relationship.*p<0.05; **p<0.01; ***p<0.001.

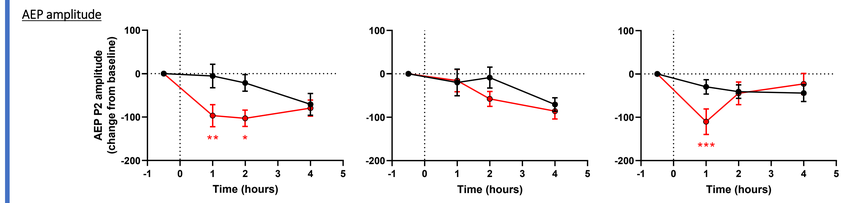

Figure 7. Auditory evoked potential amplitude is reduced by lacosamide and tapentadol (NB the lack of change with pregabalin is likely due to variable drug exposure (as shown in figure 6)). Following lacosamide administration the AEP effects follow a similar time course to the LEP modulation, however post-tapentadol the LEP and behavioural effects outlast the AEP changes This suggests that initially the putative analgesic effect is confounded by non-specific effects of tapentadol, however at 2 hours the effects are likely more restricted to the nociceptive system.

Conclusions

- Using a combination of novel technologies (wireless EEG, laser-safe stimulation enclosure), it is possible to record LEPs from awake, freely moving rodents, thereby avoiding confounds associated with anaesthesia.
- LEP amplitude can be modulated by lacosamide, pregabalin & tapentadol. Where equivalent human data exists, such as for pregabalin,(Schaffler et al. 2017 & Schaffler et al. 2018) the effects appear comparable. Further assessment of the translatability of these results will be made as additional clinical data is generated as part of the IMI-PainCare (BioPain) consortium.
- If the results of these standard-of-care compounds are translatable between species it raises the possibility LEPs could be employed as a target-engagement biomarkers in subsequent clinical trials of novel analgesics.

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