ASSESSEMENT OF SEIZURE ACTIVITY IN THE TELEMETERED DOG: A NEW PROCEDURE USING THE RODENTPACK SYSTEM

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INTRODUCTION

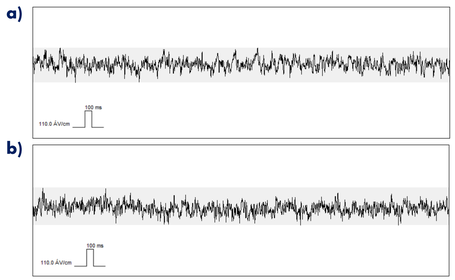
Studies on proconvulsant risk represent an important step in the drug development process, even if they are not included in the core battery for safety pharmacology. Evaluation in the dog may complement rodent studies, as it facilitates the simultaneous analysis of both neuronal and non-neuronal parameters within a single experiment. The aim of this study was to validate the use of a novel telemetry system in the dog, usually recommended for applications in the rat.

METHODS

- **Treatment:** Pilocarpine (5mg/kg/min) was dispersed in 0.2% hydroxypropylmethylcelluose in physiological saline and was administered by intravenous infusion (9 mL/kg/hour) using a perfusor. Gamma-butyrolactone (GBL) was dissolved in distilled water and was administered orally at 1000 mg/kg.
- **Surgery:** Two dogs were implanted with two surface electrodes placed over the fronto-parietal cortex. The electrodes were connected to small plugs, placed into a connector and the whole assembly was secured on the skull of the animal with dental cement. After surgery, a collar was placed around the neck of the dog to protect the implant, until the end of the experiment.
- **EEG and video monitoring:** A rodentPACK telemetry transmitter (EMKA Technologies) was plugged to the head connector. All generated data was acquired and analysed using the EMKA Technologies software (IOX version 2.8.2.10 and ECG-Auto version 2.6.0.20). The quality of the signals was checked in restrained or non-restrained conditions. Behavior/Presence of convulsions was confirmed using video-recordings.
- **Restrained conditions:** The dogs were placed in a sling during EEG recordings. As soon as the first convulsive symptoms/seizure activity were observed, an intravenous bolus of diazepam (0.2 mL/kg, 1 mL/kg) was administered.
- **Non-restrained conditions:** The dogs were placed individually within their home cage close to a telemetry receiver and both EEG and video were continuously recorded.

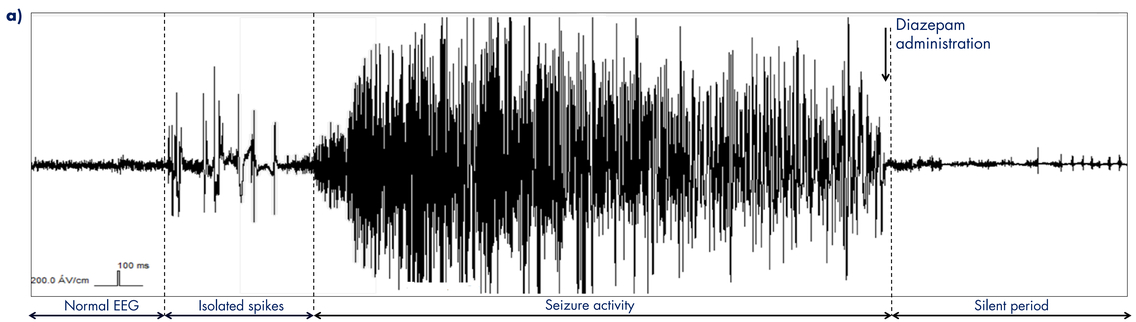
RESULTS

Figure 1. EEG recordings in control conditions



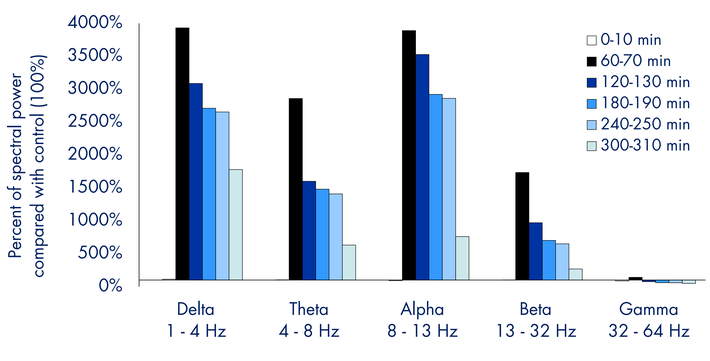
➢ a) Baseline EEG signal in restrained conditions.
b) Baseline EEG signal in non-restrained conditions.

Figure 2. EEG recording after administration of treatments

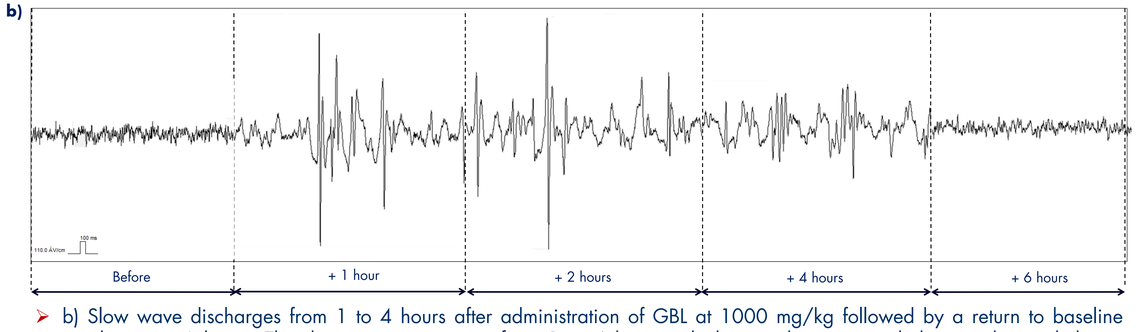


➢ a) Seizure activity after administration of pilocarpine at 125 mg/kg. Isolated spikes were accompanied of myoclonic convulsions over a period of 2 minutes, just before the occurence of clonic-tonic convulsions during seizure activity. Silent period with EEG signal of low amplitude was observed after the administration of Diazepam.

Figure 3. Spectral EEG analysis after administration of GBL



➢ Clear increase of low-middle frequencies (delta, theta, alpha and beta) whereas high frequencies (gamma) were not affected.



➢ b) Slow wave discharges from 1 to 4 hours after administration of GBL at 1000 mg/kg followed by a return to baseline conditions at 6 hours. The dog was unconscious from 1 to 4 hours, which is a characteristic behavior observed during absence seizure.

CONCLUSION

The use of the rodentPACK system with synchronized video in the dog can be a valuable tool for the assessment of proconvulsant risk of novel pharmacological substances in the context of safety pharmacology studies in the dog. The use of this system in non-restrained conditions may be advantageous in limiting the impact of stress on brain activity and allowing for an increase in the duration of EEG recording. When there is a high probability of seizure, the restrained conditions should be preferred for ethical reasons.

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