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A new method to model electroconvulsive therapy in rats with increased construct validity and enhanced translational value

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ABSTRACT

Electroconvulsive therapy is the most effective therapy for major depressive disorder (MDD). The remission rate is above 50% in previously pharmacoresistant patients but the mechanisms of action are not fully understood. Electroconvulsive stimulation (ECS) in rodents mimics antidepressant electroconvulsive therapy (ECT) in humans and is widely used to investigate the underlying mechanisms of ECT. For the translational value of findings in animal models it is essential to establish models with the highest construct, face and predictive validity possible. The commonly used model for ECT in rodents does not meet the demand for high construct validity. For ECT, cortical surface electrodes are used to induce therapeutic seizures whereas ECS in rodents is exclusively performed by auricular or corneal electrodes. However, the stimulation site has a major impact on the type and spread of the induced seizure activity and its antidepressant effect. We propose a method in which ECS is performed by screw electrodes placed above the motor cortex of rats to closely simulate the clinical situation and thereby increase the construct validity of the model. Cortical ECS in rats induced reliably seizures comparable to human ECT. Cortical ECS was more effective than auricular ECS to reduce immobility in the forced swim test. Importantly, auricular stimulation had a negative influence on the general health condition of the rats with signs of fear during the stimulation sessions. These results suggest that auricular ECS in rats is not a suitable ECT model. Cortical ECS in rats promises to be a valid method to mimic ECT.

1. Introduction

Electroconvulsive therapy (ECT) is the most effective therapy for pharmacoresistant major depressive disorder (MDD) (The UK ECT Review group, 2003; Heijnen et al., 2010). The use of ECT has constantly increased over the last decade but still the mechanisms of action are not fully understood. Clarification of the underlying mechanism leading to the therapeutic effect of ECT could significantly contribute to the understanding of the pathogenesis of MDD and the development of improved treatment strategies. Although new possibilities open up for non-invasive investigations in humans with improving imaging techniques many questions can only be addressed in animal models using invasive methods. A prerequisite to obtain data from animal research with high translational value is the validity of the model. Already in 1969, McKinney and Bunney proposed validating criteria to evaluate the translational value of models for mental diseases. Willner (1984) applied these criteria on animal models of depression which lead to an ongoing effort to improve such models for the highest validity possible. Electroconvulsive stimulations (ECS) in rats or mice are used to mimic ECT. Although ECS is a model for a treatment method and not a model for depression it is not less important to fulfil the validating criteria to obtain a high translational value. So far, experimental research is based almost exclusively on models in which rodents are treated with electroconvulsive stimulations (ECS) via auricular or, less often, corneal electrodes. In the clinical ECT setting the electrical stimulation is performed via cortical surface electrodes. It is well known that the electrode placement has a significant impact on the consequences of the induced seizure activity with respect to various parameters such as seizure type, pharmacological responsiveness and biochemical changes (e.g. Browning and Nelson, 1985; Isaak

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et al., 1985; Ferraro et al., 1990; Löscher et al., 1991). Therefore, it is more than likely that the different placement of stimulation electrodes in humans and rodents has a significant impact on the translational value of the results because the construct validity of ECS in rodents is not given. The aim of the present study is to propose an ECS method in rats using cortical screw electrodes placed above the frontal cortex which simulates the bifrontal ECT in humans. The cortical ECS was compared with the traditional auricular ECS with respect to seizure parameters and acute and chronic effects on well being and behaviour of the rats.

2. Material and methods

2.1. Animals

Male Wistar rats (9 weeks) were purchased from Janvier (Saint Berthevin, France) and housed in groups under controlled environmental conditions.

All rats were adapted to the laboratory and habituated to handling for at least one week before starting the experiments. Experiments were done in compliance with the European Communities Council Directive of 24 November 1986 (86/609/EEC) and were approved by the animal subjects review board of our institution. All efforts were made to minimize pain or discomfort of the animals used.

2.2. Implantation of screw electrodes

Thirty three rats were anaesthetized with isoflurane (1.5–3.0%) and local with tetracain and bupivacain. Buprenorphine was used for postoperative analgesia (0.045 mg/kg i.m., Temgesic®, Essex Pharma GmbH). Electrodes were placed bilaterally above the frontal cortex (AP, +2.7 mm; L, ± 4.0 mm) according to the atlas of Paxinos and Watson (2007). A reference electrode was placed above the right parietal cortex (AP, −2.0 mm; L, −2.0 mm) to allow EEG recordings. Screw electrodes were fixed with one and a half turn in the skull, so that the tip of the screw was right above the cortex without touching it. Recovery time after surgery was 2 weeks.

2.3. Electroconvulsive stimulation

Implanted rats were randomly assigned to treatment groups, i.e., auricular stimulation ($n = 10$), cortical stimulation ($n = 12$), or sham stimulation ($n = 11$). Rats without surgery served as naïve controls ($n = 9$).

ECS was delivered once daily over five days. For auricular ECS the stimulus was applied via ear-clip electrodes using the ECT Unit 57800 device (Ugo Basile, Comerio, Italy). One of the two electrodes is attached to one ear and the other one to the other ear. Cortical ECS was performed via the two frontal screw electrodes using the A310 Accupulser (World Precision Instruments, Sarasota, USA). The stimulus consisted of bidirectionally applied square wave pulses. In pilot studies we determined stimulus parameters that induce generalized seizures of at least 15 s duration in the EEG in all rats. Parameters for auricular ECS stated in the literature vary between studies. Frequency and pulse width were chosen according to literature data (Biedermann et al., 2012; Newton et al., 2003). Stimulus duration and current intensity were validated in preliminary experiments. We started with stimulus duration of 0.2 s and 50 mA current intensity corresponding to a charge of 1.8 mC. With these parameters none of the rats developed a seizure. We then stepwise increased current intensity to 70 mA without seizure induction but the rats exhibited hyperlocomotion after the stimulus. Next we increased stimulus duration to 0.5 s and stepwise increased current intensity from 40 to 70 mA. All rats developed generalized seizures when stimulated with 70 mA. Therefore auricular ECS stimulation parameters used in this study were 0.9 ms pulse-width, 100 pulses/s, 0.5 s duration, 70–82 mA. This corresponds to a charge of 6.3–7.4 mC. For cortical ECS, current intensity was stepwise increased from 2.5 to 7.0 mA in preliminary experiments. The other stimulus parameters were chosen on the basis of clinical data (Department of Psychiatry, Medical School Hannover, Germany). Parameters for cortical ECS were 1 ms pulse-width, 100 pulses/s, 1 s duration, 7–10 mA which corresponds to a charge of 1.4–2.0 mC. The charge was calculated using the formula: *charge = pulse width [s] × (frequency [Hz] × 2) × stimulus duration [sec] × current intensity [mA]* (Andrade et al., 2002).

For EEG recordings a one-channel amplifier (ADInstruments Ltd., Sydney, Australia) and an analogue-digital converter (PowerLab/800s, ADInstruments) were used. The duration of the seizure in the EEG and the seizure type were determined. Control and sham animals underwent the same handling procedure without electrical stimulation.

2.4. Determination of the effects of ECS

Body weight was determined before and after ECS sessions as a measure for the general condition. A reduction in body weight points to a reduced well-being of the rats. Ultrasonic vocalisation was recorded via Avisoft recorder (version 3.4.2, Avisoft Bioacoustic, Berlin, Germany) for 5 min during most of the ECS sessions, starting 1 min before stimulation. Number and duration of 22 kHz-calls which are associated with distress and fear of rats (duration: >20 ms; frequency: 18–32 kHz) (Portfors, 2007) were analysed.

The forced swim test (FST) was performed according to Porsolt et al. (1977) to evaluate the behavioural effect of ECS. Rodents were individually placed in a transparent plexiglas cylinder (50 cm deep, 25 cm diameter) containing 20 cm of water (25 ± 1 °C). Two days before beginning of the ECS sessions a 15 min pre-test trial was performed followed by a 5 min test trial 24 h later. The retest trial (5 min) was performed 48 h after the last of a series of 5 daily ECS. Behaviour was recorded with an HD-camcorder (Canon Legria HFS21) and the immobility time (making only those movements necessary to keep the head above the water) for each rat during the first 5 min of the pre-test, the test and the retest trial was quantified. The immobility time of each rat during the trials was quantified.

To ensure that seizures did not have an effect on mobility of the rats per se, locomotor activity was measured 24 h after the last stimulation in a round open field made of black PVC (diameter 80 cm, height 80 cm). Distance moved and velocity was recorded for 5 min and analysed with EthoVision®XT7 software (Noldus Information Technology, Wagening, the Netherlands).

For the performance and analysis of the forced swim and open field test and for determination of body weights the experimenter was blinded to the treatment groups. The analysis of seizure duration in the EEG and ultrasonic vocalization was also performed blinded. For evaluating the seizure type the experimenter was aware of the stimulation method used.

2.5. Statistical analyses

Depending on whether data were normally distributed or not, either parametric or nonparametric tests were used for statistical evaluation. In case of more than two groups, analysis of variance (ANOVA) with post hoc testing was used. Fisher's exact test was used to compare the occurrence of 22 kHz-calls during ECS. All statistical analyses were performed with the Prism 5 software from