Phenotyping the DISC1 rat model of Schizophrenia using PPI, amphetamine-induced hyperlocomotion, sleep-EEG and 40Hz ASSR

Transpharmation
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[1]John Huxter, [2]Ashley M. Bernardo, [2]Lukasz Dlugosz, [2]Lauren Stam, [2]Sandy Thevarkunnel, [3]Carsten Korth, [2]Guy Higgins

[1]Transpharmation UK, [2]Transpharmation Canada, [3]Heinrich Heine Univ. Dusseldorf, Germany

hhu Heinrich Heine Universität Düsseldorf

INTRODUCTION

Schizophrenia is a devastating lifelong psychiatric condition for which there is currently no cure, and symptomatic treatments with varying degrees of efficacy and side-effects. Presence of the Disrupted in Schizophrenia 1 (DISC1) protein is a known risk factor for schizophrenia, and in the tgDISC1 rat, overexpression of the DISC1 transgene produces neuronal DISC1 aggregates and a number of phenotypes consistent with the human condition. Here we describe additional phenotyping of the model using behaviour and electrophysiology (EEG). Analysis was also performed to identify any correlations between behavioural outputs and EEG measures.

METHODS

Nine male tgDISC1 rats and seven male littermate controls were tested in pre-pulse inhibition (PPI), sleep-EEG, 40 Hz auditory steady-state response (ASSR), and amphetamine-induced hyperlocomotion (0.3mg/kg IP). An atypical antipsychotic (risperidone 0.3 mg/kg s.c.) was used as a reversal agent.

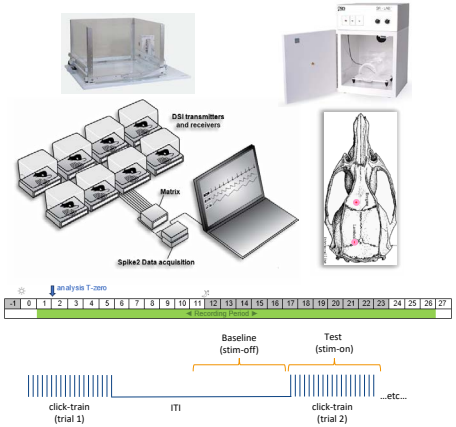

Figure 1. LMA was recorded in an LMA chamber with infrared beams. PPI was competed in a startle response chamber and all EEG (sleep and ASSR) was recorded using DSI transmitters and receivers. The timeline for EEG sleep recording is shown followed by a simple example of ASSR.

RESULTS

Behaviour

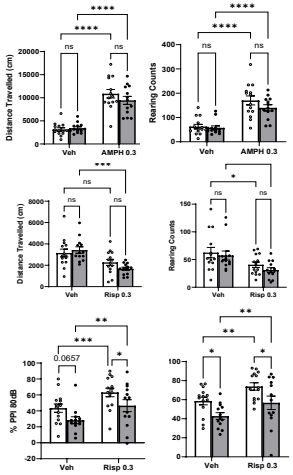

Figure 2. LMA and Amphetamine. Amphetamine increased locomotor activity in all animals as expected. DISC-1 animals were not hypersensitive.

Figure 3. LMA and Risperidone. Risperidone had some sedative effects on LMA. No significant effect of genotype.

Figure 4. PPI and Risperidone. PPI showed deficits of in the DISC-1 animals and Risperidone was able to partially reverse this deficit.

EEG

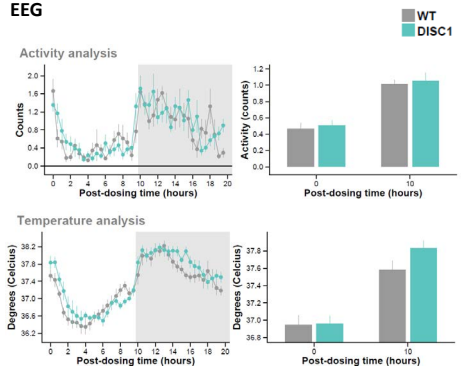

Figure 5. LMA and Temperature EEG. Locomotor activity and core body temperature measured during the EEG recording revealed no significant differences between the WT and DISC-1 transgenic animals.

RESULTS

Figure 6. Sleep EEG. Consistent reductions in qEEG power were seen in DISC-1 compared with WT animals. These were significant for 1-4Hz delta (wake and REM sleep), 4-10Hz theta (REM sleep) and 30-50Hz gamma (waking).

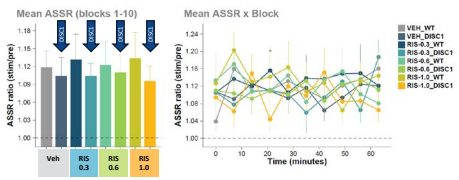

Figure 7. ASSR and Risperidone. No significant difference was found on the ASSR ratio between genotypes. Risperidone itself had no effect on ASSR.

RESULTS

Figure 8. Correlations (red boxes=significant). Rearing was corelated with distance startle. Startle was negatively correlated with PPI. Interestingly, waking theta was negatively correlated with distance and startle, but positively correlated with PPI, reflecting the genotypic differences on these measures. The theta-PPI correlation was also significant within the WT group within wildtype animals (r=-0.790*).

CONCLUSIONS

- TgDISC-1 animals did not show amphetamine hypersensitivity
- PPI showed deficits in tgDISC-1 animals and Risperidone was able to partially reverses these deficits
- Body temperature and spontaneous behaviour in the sleep-EEG assay did not differ from the littermate controls
- TgDISC-1 rats show reduced theta and delta bands during REM sleep
- No genotype differences were found in ASSR

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