Mismatch Negativity in rats
A translational model in schizophrenia research

Neil Upton[1], Graham Wadsworth[1], Dave R. Anderson[2], Timothy Piser[2], Steven C. Leiser[2]
[1]Transpharmation Ltd, London, United Kingdom; [2]Cadent Therapeutics, Cambridge, MA, USA

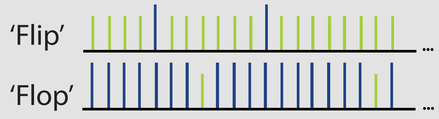
Transpharmation
Science that translates into results

Introduction

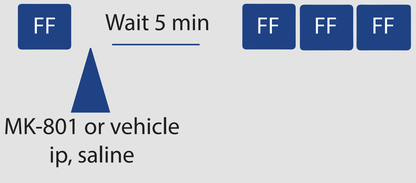
Mismatch negativity (MMN) is a component of event-related potentials (ERP) recorded in the scalp EEG. MMN is diminished in many neuropsychiatric disorders including schizophrenia. Interestingly, antagonists of the N-Methyl-D-aspartate (NMDA) receptor, such as ketamine, mimic symptoms of schizophrenia and also disrupt MMN in healthy volunteers. MMN reflects pre-attentive processing and is elicited clinically by an auditory oddball paradigm in which a physically different, deviant ('oddball'; DEV) stimulus occurs infrequently and unexpectedly within a sequence of repetitive identical ('standard'; STD) stimuli. Critically, MMN can be measured in rodents and thereby represents a potential translational marker that can be used for testing novel treatments for neuropsychiatric disorders.

Methods

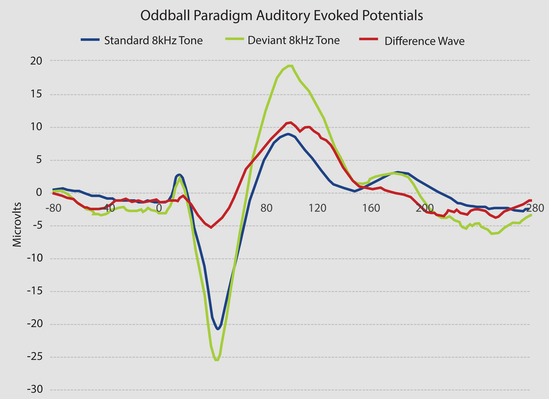
EEG surgery and recording
We implanted 18 adult (180-200g), male Sprague Dawley (SD) rats with EEG electrodes under isoflurane (2-5%) anesthesia. Briefly, we placed a telemetry transmitter (F40-EET; DSI, USA) into the peritoneal cavity and the tip of EEG leads epidurally over the frontal cortex (1.0 mm lateral and 2.0 mm anterior to Bregma) and cerebellum. After recovery, the rats were placed individually in sound attenuated recording chambers, equipped with audio speakers. EEG signals were analogue filtered (1-50 Hz), then sampled at 1kHz (Micro1401-3; CED, UK) and stored on a PC for offline analysis (Spike2; CED, UK). Tonal stimuli were generated by a custom sequencer script and their timestamps were recorded together with the EEG signal.



Flip-flop' oddball paradigm
"Flip-flop" blocks were presented consecutively, in which the first "flip" sequence consisted of 1000, randomized, 50 ms long tones of either 6.0 kHz (STD; 90% probability, 900 tones) or 8.0 kHz (DEV; 10% probability, 100 tones). The subsequent "flop" sequence consisted of the same number of tones, but the frequencies were reversed: the 6.0 kHz tone became the DEV, and the 8.0 kHz tone became the STD. The interstimulus interval was 350 ms. After one block of 'flip-flop' the animals were treated with the NMDA antagonist MK-801 (0.1, 0.3 and 0.5 mg/kg, i.p.; Sigma-Aldrich, UK) or its vehicle (saline, 1 ml/kg) that was followed by three blocks of 'flip-flops' (see below).



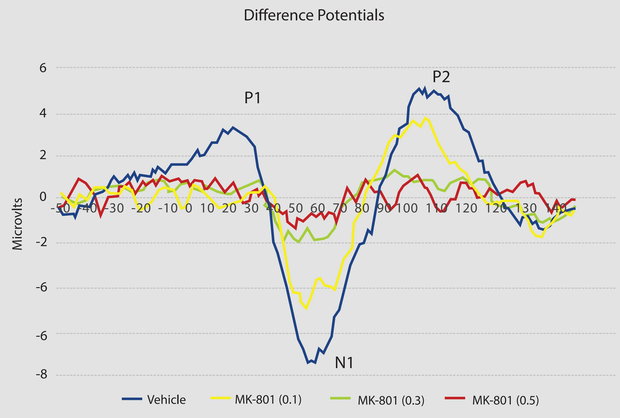
Data Analysis



ERP's were generated for standard and deviant stimuli by averaging EEG waves between -100ms +250ms of tone onset. Then difference (DIF) waves were calculated by subtracting the STD waves from the DEV waves (see above). Peaks and throughs were identified in STD, DEV and DIF waves as follows: P1 = max. value between 0-30ms, N1 = min. value between 20-60ms, P2 = max. value between 50-150ms. Furthermore, the area under the curve (AUC) between 30-60ms (N1 AUC) and 60-120ms (P2 AUC) after tone onset was determined. Distances between P1 and N1 and between N1 and P2 were also calculated.

Results

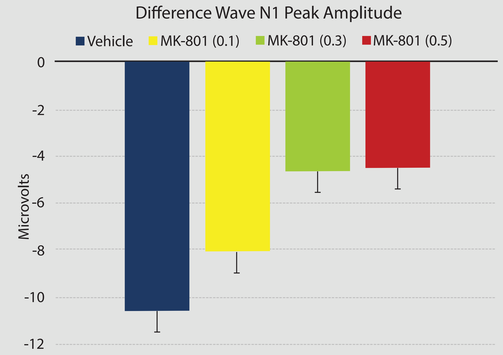
1. The NMDA antagonist MK-801 disrupts MMN in SD rats



MK-801 (0.1, 0.3 and 0.5 mg/kg i.p.) dose-dependently disrupted MMN in SD rats 40-60 minutes post dose that is shown by the decrease in difference potentials after drug treatments compared to vehicle treatment.

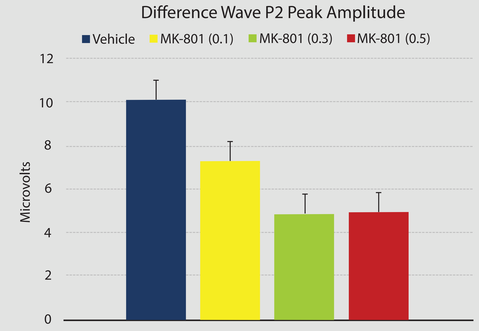
Results

2. MK-801 reduced the magnitude of N1 of the difference wave



MK-801 (0.1, 0.3 and 0.5 mg/kg i.p.) dose-dependently reduced N1 amplitude in SD rats 40-60 minutes post dose compared to vehicle treatment.
*p<0.05 Fisher post-hoc test vs. Vehicle

3. MK-801 decreased the amplitude of P2 of the difference wave



MK-801 (0.1, 0.3 and 0.5 mg/kg i.p.) dose-dependently reduced P2 amplitude in SD rats 40-60 minutes post dose compared to vehicle treatment.
*p<0.05 Fisher post-hoc test vs. Vehicle

Conclusions

- The electrophysiological correlate of clinical MMN can be measured in rats.
- Similar to humans, NMDA antagonists such as MK-801 impair MMN in rats.
- MMN may be a valuable translational tool for testing therapeutics targeting neuropsychiatric disorders including schizophrenia.