The NMDAr positive allosteric modulator CAD-8688 reverses mismatch negativity impairments in the rat sub-chronic PCP model of schizophrenia

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Introduction

Converging lines of clinical evidence suggest that hypofunction of the glutamatergic N-methyl-D-aspartate receptor (NMDAr) is implicated in the pathogenesis of schizophrenia. NMDAr antagonists such as phencyclidine (PCP) exacerbate psychotic symptoms in schizophrenic patients, and mimic schizophrenia in healthy volunteers. Auditory novelty-detection is an NMDAr-dependent process that is associated with an auditory-evoked potential (AEP), the Mismatch negativity (MMN). MMN is reduced in schizophrenic patients and may represent a biomarker of NMDAr hypofunction in schizophrenia. The aim of this study was to determine whether sub-chronic PCP treatment impairs MMN and, if so, whether these deficits can be reversed by an NMDAr positive allosteric modulator (PAM: CAD-8688).

Methods

EEG surgery and recording

23 adult (200-250 g) male LH rats (Envigo, UK) were surgically implanted with telemetry transmitters for fronto-parietal EEG and EMG recording. 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 parietal cortex (1.5 mm lateral and 0.0 mm anterior from Lambda) under isoflurane (2-5%) anesthesia. 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

MMN was elicited in awake, freely-behaving rats by the auditory 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% protbability, 100 tones). The subsequent "flop" sequence consisted of the same number of tones, but the frequencies were reversed. The interstimulus interval was 350 ms. The difference (DIF) waves were generated by subtracting STD waves from DEV waves. AEP components were measured in STD, DEV and DIF waves.

Methods

Drug treatment and MMN recordings

After recording baseline MMN, rats were treated with phencyclidine (PCP) (5 mg/kg, i.p.) twice daily for seven days. MMN was tested after the first and last treatment with PCP, as well as after a seven days washout period (not presented here). After nine days of washout, the rats were treated acutely with vehicle (5 ml/kg, p.o.; n=13) or CAD-8688 (3 mg/kg, p.o.; n=10). One hour after treatment, three blocks of 'flip-flops' (FF) were presented to the rats and their EEG was recorded. The EEG during the 2nd and 3rd FF blocks was used for data analysis.

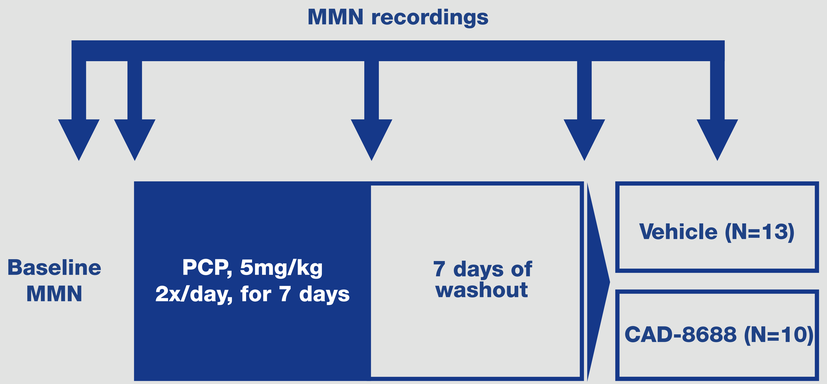

Figure 1 Study design.

Results

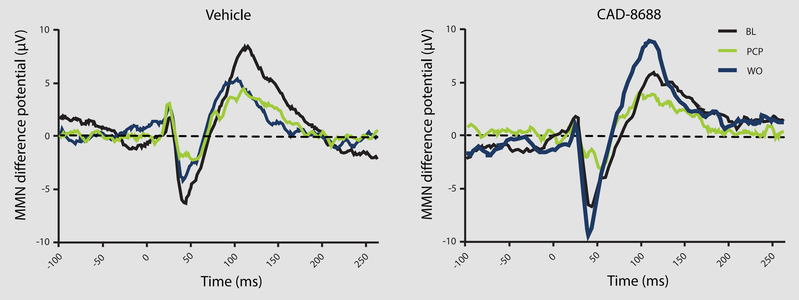

Figure 2 Treatment with CAD-8688 (3 mg/kg), but not with its vehicle, reversed the deficit in MMN caused by phencyclidine (PCP). A baseline (BL) recording was made before initiating sub-chronic phencyclidine (PCP) treatment. The effect of CAD-8688 or its vehicle on MMN was assessed on the 9th day of the washout (WO) period. Data are presented as mean in 1 ms interval.

Results

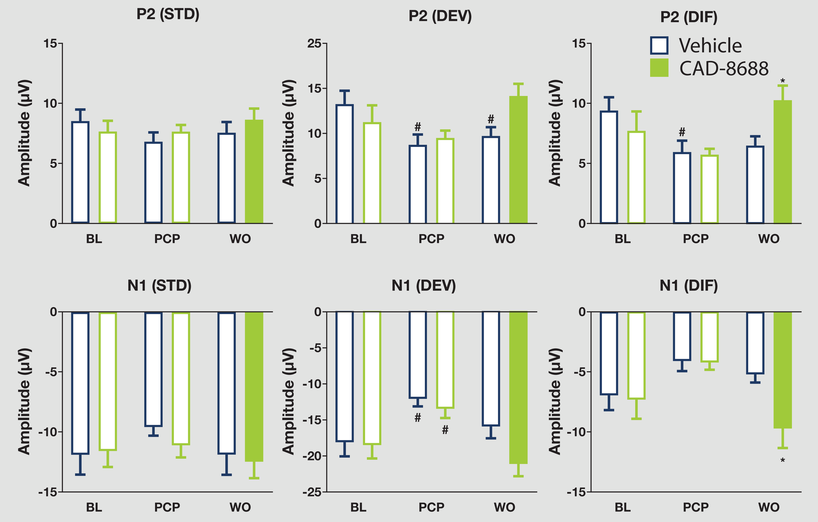

Figure 3 CAD-8688 reversed the effect of PCP on N1 and P2 components of the difference (DIF) waves. Sub-chronic PCP treatment reduced both N1 and P2 amplitudes in deviant (DEV) waves, but not in standard (STD) waves, and this effect was reversed by CAD-8688. Data are presented as mean ± SEM. *P<0.05 compared to vehicle (Sidak post-test); # P<0.05 compared to BL (Dunnett post-test).

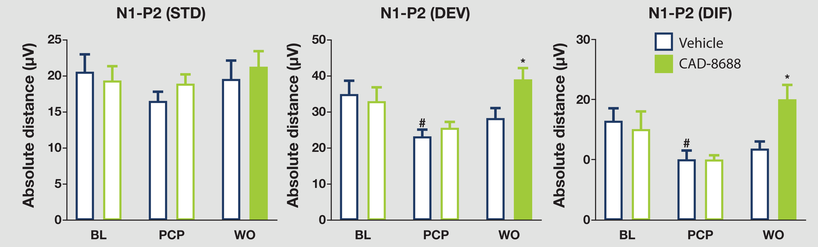

Figure 4 Sub-chronic PCP treatment reduced N1-P2 distances in difference (DIF) waves that was reversed by CAD-8688. Compared to vehicle treatment, CAD-8688 increased N1-P2 distances in deviant (DEV) waves, but not in standard (STD) waves. Data are presented as mean ± SEM. *P<0.05 compared to vehicle (Sidak post-test); # P<0.05 compared to BL (Dunnett post-test).

Conclusions

- Schizophrenia-like MMN deficits are induced in the rat by sub-chronic PCP treatment.
- The PCP-induced deficits in MMN persist after drug washout, which makes this model a powerful translational tool for testing novel therapeutics targeting schizophrenia.
- Reversal of the PCP-induced deficits in MMN by CAD-8688 suggests a therapeutic potential to restore NMDAr hypofunction in patients with schizophrenia.