NMDA receptor antagonist-induced changes in rat EEG power spectra as a model of schizophrenia

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Introduction

Schizophrenia is a debilitating neuropsychiatric disorder characterised by an array of symptoms, with negative symptoms (e.g. lack of emotion) and cognitive dysfunction proving resistant to current therapies.

Recent EEG studies have provided evidence that changes in synchronicity in the Gamma range (30-80Hz) are associated with this treatment resistance in schizophrenic patients.

A large body of evidence now points to the disruption of N-methyl-D-aspartate (NMDA) mediated signalling as a core pathophysiological hallmark in schizophrenia, including the observation that pre-clinical species administered NMDA antagonists display a phenotype consistent with schizophrenia.

Aims

In this study we investigated the effects of two NMDA antagonists, ketamine (KET) and phencyclidine (PCP) on EEG spectral power and sleep-wake stages in freely moving rats.

Methods

EEG signals were recorded from electrodes over the frontal-parietal cortex using intracranial electrodes, with the positive electrode at 2mm left of the mid-line, 2mm anterior of Bregma and the negative electrode 2mm left of the mid-line, 2mm anterior of lambda. Nuchal EMG was recorded to enable sleep stage scoring. Signals were recorded from the onset of the light period for 24hrs. The animals were dosed in a 'latin square' design receiving either vehicle (saline s.c.), KET (3, 10, 30mg/kg, s.c.) or PCP (0.3, 1, 3mg/kg, s.c.) 30min following the onset of the light period. Sleep stages were defined as below:

Sleep Stage	Definition
Active Wake	EMG integral greater than 4 fold minimum; Activity count ≥ 1
Quiet Wake	EMG Integral greater than 4 fold minimum; Activity count = 0
Sleep Stage 1	EMG Integral between 2 & 4 fold minimum; Delta Power < 45%
Sleep Stage 2	EMG Integral between 2 & 4 fold minimum; Delta Power ≥ 45%
Paradoxical sleep	EMG between minimum and 2 fold minimum; Theta power ≥ 45%

Power spectra bands were calculated from the raw EEG signal using Fast Fourier Transformation and the following frequency banding:

Spectral Band	Frequency Range (Hz)
Delta	0.25 to 4
Theta	4 to 8
Alpha	8 to 13
Beta	13 to 40
Gamma	40 to 80

Data are expressed as the area under the curve (AUC) over the period of peak effect for each treatment.

Results

Fig.1. Ketamine and PCP both induced stimulation of locomotor activity as measured by activity counts

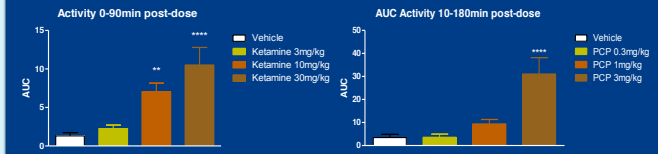


Fig.2. Ketamine and PCP both induced arousal in the rats, increasing wake and decreasing all sleep stages

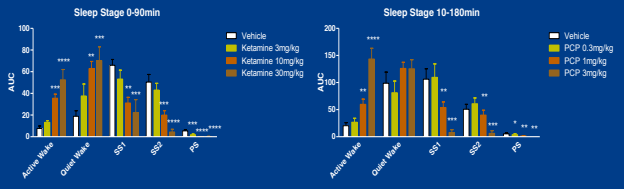


Fig.3. Ketamine and PCP both demonstrated a shift away from lower frequencies toward the high frequency bands, with a profound increase in Gamma

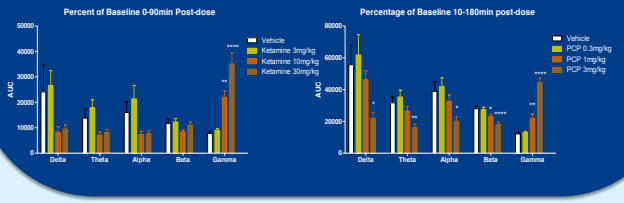
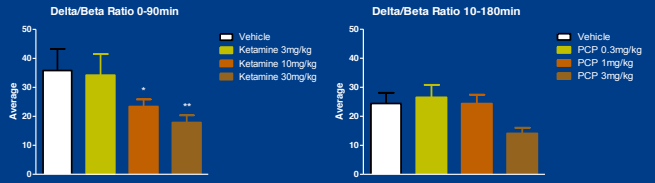


Fig.4. Ketamine produced a robust reduction in the Beta/Delta ratio. PCP failed to induce any statistically significant changes in Delta/Beta ratio, although there was a strong trend toward a reduction at 3mg/kg



*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 cf vehicle treated animals

Conclusion

- Both PCP and Ketamine caused profound changes in the behavioural and EEG profiles of the animals.
- Activity was increased.
- Sleep-wake was shifted to an arousal profile with an increase in wake phases and decrease in all sleep phases.
- In terms of EEG power, PCP and Ketamine dramatically increased gamma frequencies.
- Delta/Beta ratio, which is negatively associated with arousal and attentional state, was reduced by Ketamine at doses that also changed behavioural state. PCP failed to reduce Delta/Beta ratio at any dose. This result may be attributed to the potential differences in underlying pharmacology/MoA between the two agents.
- These data add further weight to the use of NMDA receptor antagonists to provide a valid translational model of schizophrenia and suggest that EEG biomarkers may have utility in identifying novel treatment strategies for restoring more normal gamma synchronicity.

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