Interictal relative gamma power as a biomarker for anti-epileptic drug response in absence epilepsy

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Introduction

Childhood absence epilepsy is a form of idiopathic (genetic) generalized epilepsy characterized by ictal 3-4 Hz generalized spike and wave activity on the electroencephalogram (EEG) and behavioral arrest. Medications including carbamazepine and phenytoin are usually ineffective and can even paradoxically aggravate absence seizures1.

The NMDA receptor antagonist MK-801, while not used clinically, is effective at treating seizures in the tottering mouse model of absence epilepsy, whereas it causes a robust seizure exacerbation in stargazer mice2. This effect in stargazer mice may be due to mis-trafficking of AMPA receptors to the dendrites of parvalbumin-expressing (PV+) interneurons, leading to stronger disinhibition and aggravation of seizures.

Methods

Mice were surgically implanted bilaterally with silver wire electrodes inserted into the somatosensory cortex. EEG signals were recorded for 30 minutes, video-EEG was then collected for a 30 minute baseline sampling period, followed by intraperitoneal drug injection and the period 30-60 minutes after drug injection was analyzed. All in vivo experiments were initiated between 12-2pm.

Results

MK-801 has an opposite effect on relative gamma power in stargazer and tottering mice

As seen previously2, MK-801, an NMDA receptor antagonist, caused seizure exacerbation with irregular 3-4 Hz spike-wave discharges in stargazer mice. Using SEM, 3.46x ± 0.86x relative seizure duration, n=6, p=0.0002.

Ephoximide and 4-aminopyridine significantly reduce seizures and increase relative gamma power

(A) Significant increase in relative gamma power with 200 mg/kg ethosuximide in WT, stargazer and tottering mice.

The shift in peak interictal relative gamma power is inversely correlated with a drug’s effect on seizures

Inverse correlation between AED efficacy (mean±SEM) and change in peak relative gamma power (meanSEM, *p<0.05). Drug responses cluster into 3 groups based on relative seizure duration. Seizure aggravation (top) is associated with reduction in relative gamma power while seizure reduction (bottom) is associated with augmented relative gamma power. Drugs with no significant effect on seizures (middle) have no significant effect on gamma power. Overall, there is an inverse correlation between the mean change in relative gamma power and mean change in seizure duration for a given drug (r=0.726). Gene-linked differences between stargazer (circles) and tottering (squares) mice are apparent with administration of MK-801 (red), and flupirtine (orange).

Summary

1) There is a gene-linked baseline augmentation of beta and gamma power in stargazer mice compared to both tottering and WT mice.

2) NMDA receptor blockade leads to seizure exacerbation in stargazer but not tottering mice and normalizes the power spectrum to WT levels.

3) In both absence models, the shift in peak interictal relative gamma power is inversely correlated with a drug’s effect on seizures.

4) Relative gamma power may serve as a predictive biomarker for AED efficacy in generalized spike-wave epilepsy.

References


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