

Bexarotene reduces network excitability in models of Alzheimer's disease and epilepsy

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ABSTRACT

Epilepsy is a complex disease with diverse environmental and genetic causes, and is often comorbid with other neurological diseases such as Alzheimer's disease (AD). This makes understanding the common mechanisms between these diseases an excellent way to advance both fields of study. Recently, an anti-cancer drug and specific retinoid X receptor agonist, bexarotene, has been shown to have a beneficial impact on a mouse model of Alzheimer's disease by reducing amyloid beta levels and improving cognitive deficits. However, the effect of bexarotene on the known neuronal network hyperexcitability of Alzheimer's mouse models has not previously been investigated, and could shed light on intermediary pathogenic mechanisms.

We examined the effects of bexarotene on spontaneous cortical activity patterns in the J20 human APP mouse model of AD by EEG monitoring in awake, behaving mice. We observed that continuous oral treatment with bexarotene reduced the interictal EEG spike rate in the J20 mouse model aged 4 to 18 months. In order to further investigate this hyperexcitability reduction, we next studied a well described mouse model of epilepsy, the knockout of the voltage gated potassium channel Kv1.1. Although the Kv1.1 model does not express amyloid beta plaque pathology seen in the J20 model, we observed by video EEG that hyperexcitability, as measured by interictal spike rate, decreased over a similar course of bexarotene treatment in adult mice aged 5-10 weeks. The effects of bexarotene progressed over several days, and were reversible. When acute hippocampal slices were bathed in 7.5mM KCl to elicit synchronous spikes within the CA3 neuronal layer, application of 10 μ M bexarotene elicited a small but significant decrease in the spontaneous spike rate.

Taken together, the *in vivo* and *ex vivo* decreases in hyperexcitability in models with and without amyloid beta plaque pathology raise important implications for understanding the mechanisms and benefits of bexarotene as a cognitive enhancer.

METHODS

Simultaneous Video-Electroencephalography was performed in 23 hAPP J20 mice (14 bexarotene, 9 vehicle) and 11 Kv1.1 null (6 bexarotene, 5 vehicle) adult mutant mice using chronic tethered EEG. 100mg/kg/day bexarotene or equivalent dose saline delivered daily (Targretin® capsule dissolved in additional 2 mL of water). Spectral Analysis was performed on 30 minute EEG epochs at the same time each day. Upon import into Matlab (R2011b, Mathworks, Inc, Natick, MA), the files were processed using the frequency power spectrum density (Welch) transform. *In vitro* hippocampal slice electrophysiology used standard extracellular recording methods. 300 μ m transverse hippocampal slices were induced to burst synchronously in the CA3 hippocampal region by bathing in 7.5mM KCl. Following acquisition of stable frequency bursting, 10 μ M bexarotene was added to the slice bath, allowed to equilibrate, and the frequency of bursting was measured again.

Figure 1. Bexarotene reduces cortical epileptiform spiking in hAPP J20 model

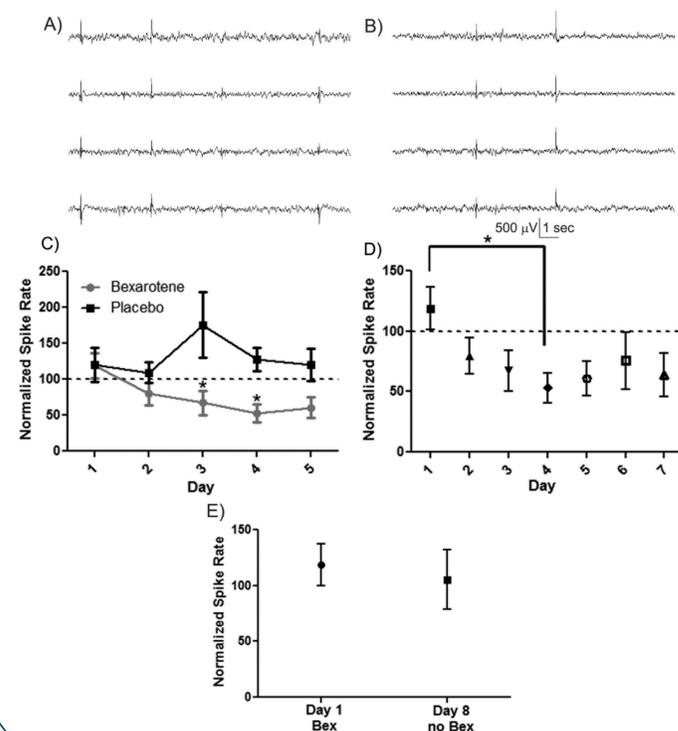


Figure 2. Bexarotene reduces cortical epileptiform spiking in Kv1.1 null model

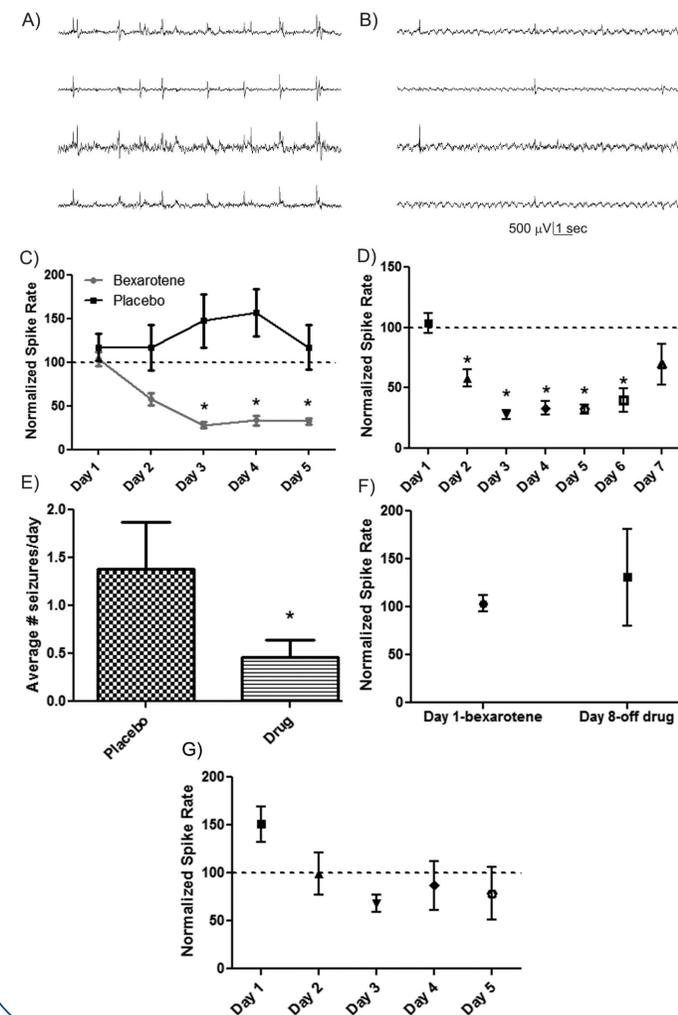


Figure 3. Bexarotene does not alter the EEG frequency distribution

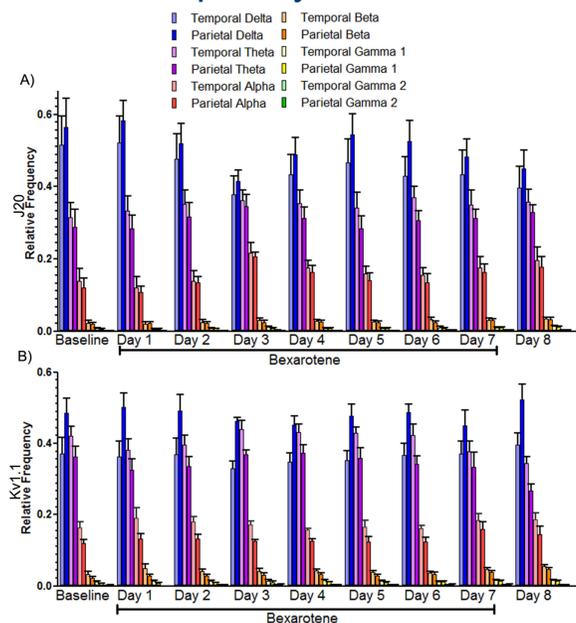
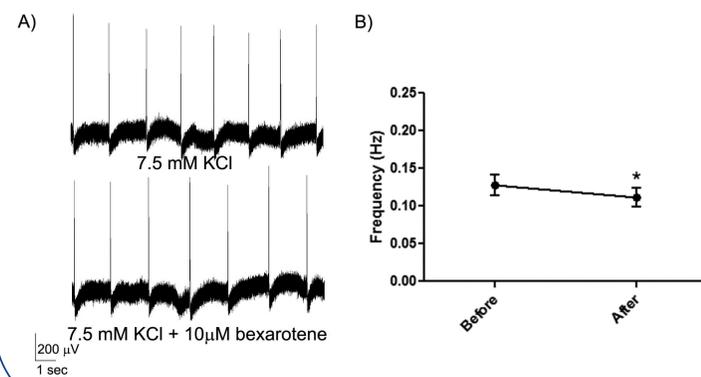


Figure 4. Bexarotene reduces *in vitro* spike bursting frequency



CONCLUSIONS

- Bexarotene reduces *in vivo* cortical epileptiform spiking in two models of epilepsy. One model has beta amyloid plaque pathology and one has no known AD pathology.

- Bexarotene rapidly reduces *in vitro* hippocampal CA3 spike bursting activity when applied to slices already bursting in 7.5mM KCl.

- Bexarotene has little effect on basal EEG spectral frequency patterns in awake and behaving mice.

- These results indicate that bexarotene shows potential for acute therapeutic benefit by reducing abnormal cortical excitability in both epilepsy and Alzheimer's models.

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Disclosure

VB, JH, JR, JN have no conflicts of interest. GL is an officer of ReXceptor, Inc which is a company engaged in commercializing bexarotene for treatment of AD. PC is a shareholder in ReXceptor, Inc.