

Functional epigenomic dissection of epilepsy

Approaches in human brain tissue and corresponding animal models

Background

- **Genetic and acquired epilepsies** can affect identical target molecules.
- **Mutational Channelopathy:** Rare deleterious gene mutations and common polygenic variation act synergistically. **Causal SNPs** in non-coding regions exert a regulatory effect on the transcriptional activity of adjacent genes by an allelic functional alteration of cis-acting epigenetic elements.
- **Transcriptional Channelopathy:** Dynamic epigenetic promoter-regulation after brain insults including status epilepticus (SE) orchestrates transcriptional dynamics that finally result in a hyperexcitable focus.

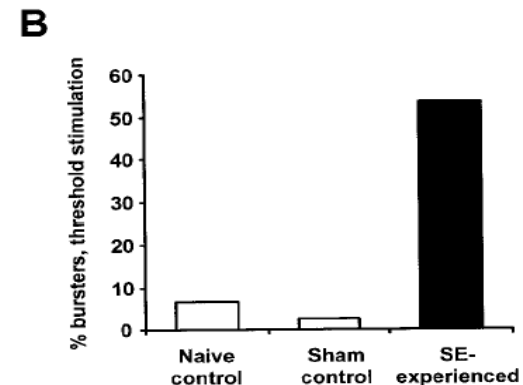
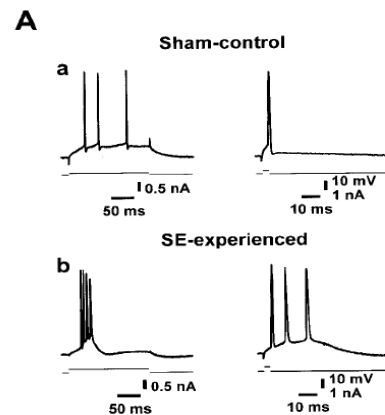
Ca_v3.2 T-type transcriptional channelopathy

Brain insult, e.g. status epilepticus (SE)

Transient transcriptional and translational augmentation of Ca_v3.2

Increased density of voltage dependent T-type Ca²⁺ currents

Augmented propensity for burst discharges in CA1 pyramidal neurons



Su et al., J Neurosci 2002

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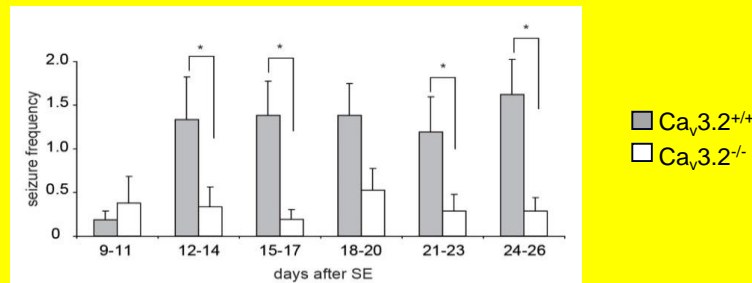
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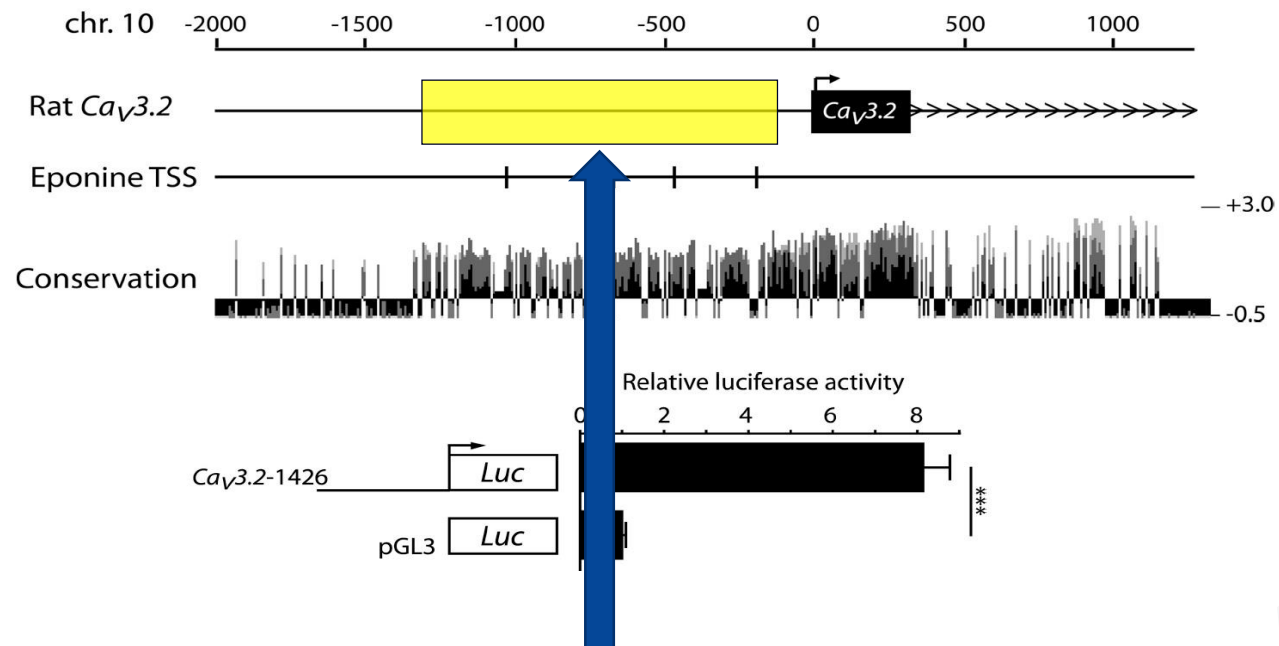


Contribution to increased seizure frequency



Becker et al, J Neurosci 2008

Promoter control of $Ca_v3.2$ channelopathy

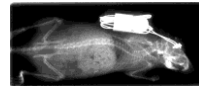


Accumulation of Zn^{2+} -inducible binding sites for transcription factor MTF1



MTF1-dominant negative effect on seizure frequency

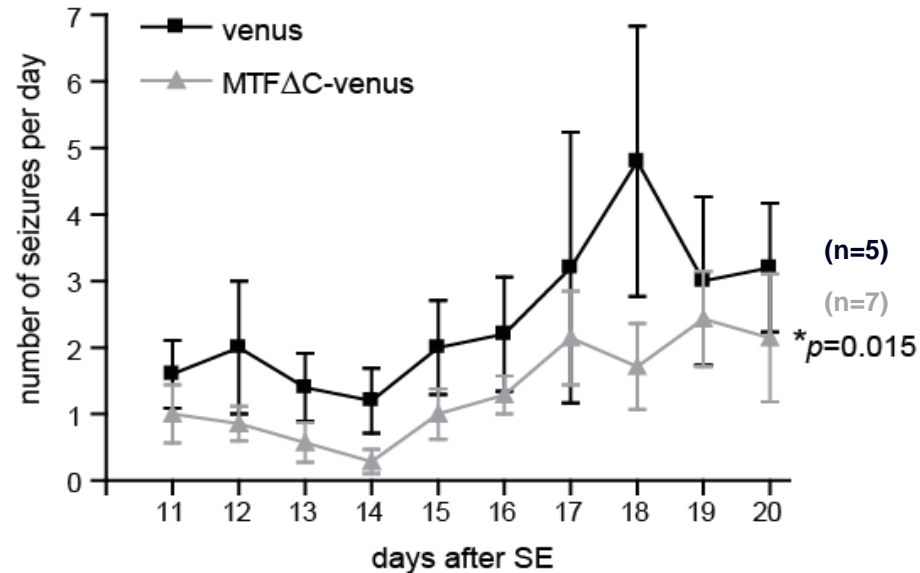
Transmitter implantation/
MTF Δ -venus rAA Virus-injection



Seizure monitoring

Time line

SE induction



Thank you!

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