Epileptogenesis- and epilepsy-associated changes in Sigma-1 expression in chronic mouse models of temporal lobe epilepsy

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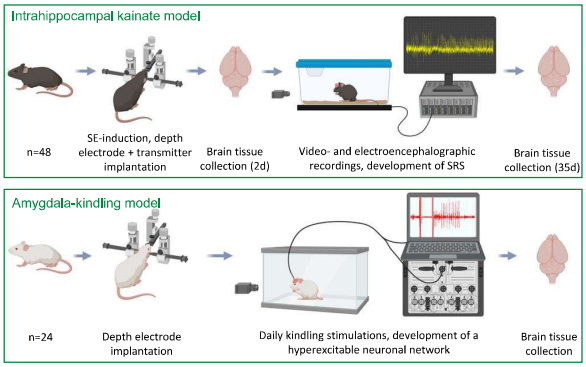
PURPOSE

Sigma-1 impacts mitochondrial function, various voltage-gated ion channels, and neurotransmitter receptors, positioning it as a potential target for epilepsy treatment. However, disease-related alterations may influence target expression and drug efficacy. Therefore, the aim of this study was to characterize Sigma-1 expression in two chronic mouse models of temporal lobe epilepsy.

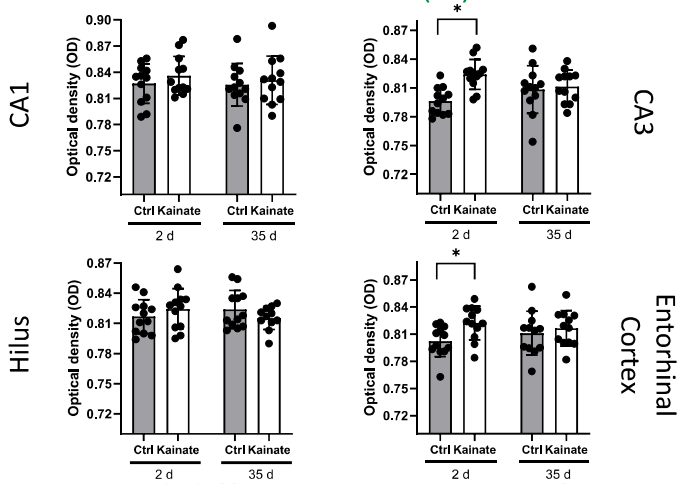
METHODS & STUDY DESIGN

Male C57BL/6JRj mice (n=48) received kainic acid (n=24) or saline (n=24) injections into the right hippocampus to induce a non-convulsive status epilepticus (SE). Brain tissue was collected two days (acute post-insult phase, n=12) or 35 days (chronic phase with spontaneous electroencephalographic seizures, SRS, n=12) after SE.
In the kindling model, female NMRI mice (n=24) received suprathreshold stimulations of the right Amygdala until they exhibited ten generalized seizures (n=12). Sham-stimulated mice served as controls (n=12).
Subsequently, the cellular expression pattern of Sigma-1 was examined in both models by immunohistochemistry, and in the kainate model also by quantitative PCR (qPCR).



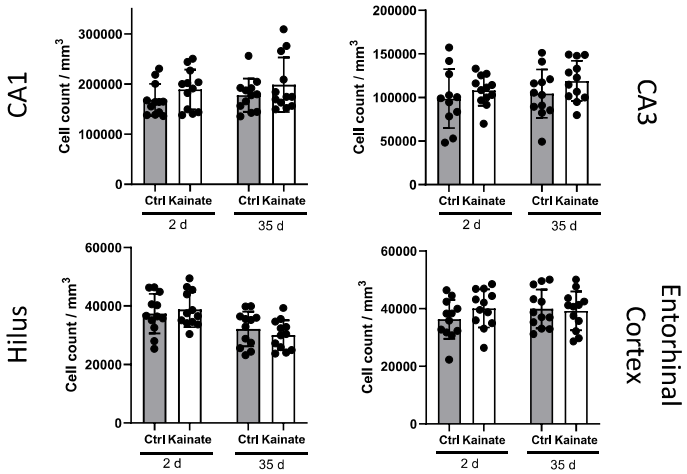
RESULTS

OPTICAL DENSITY (OD)



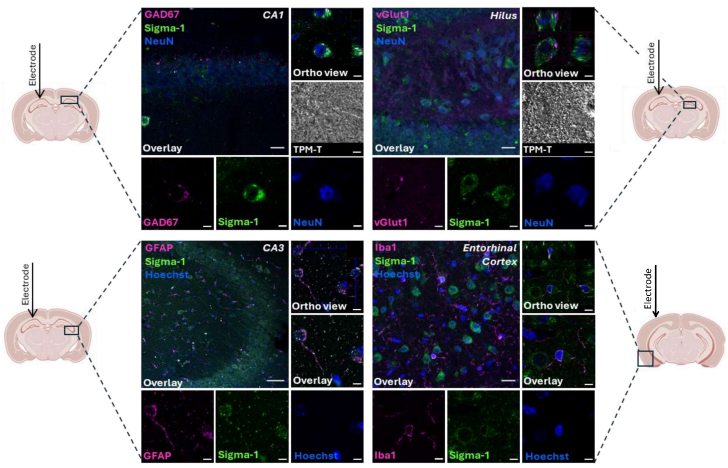
The optical density (OD) of Sigma-1 remained unchanged in most of the brain areas investigated. In the kainate model, an increase was demonstrated in the CA3 region of the Hippocampus and in the Entorhinal Cortex two days post SE.

STEREOLOGICAL CELL COUNTING



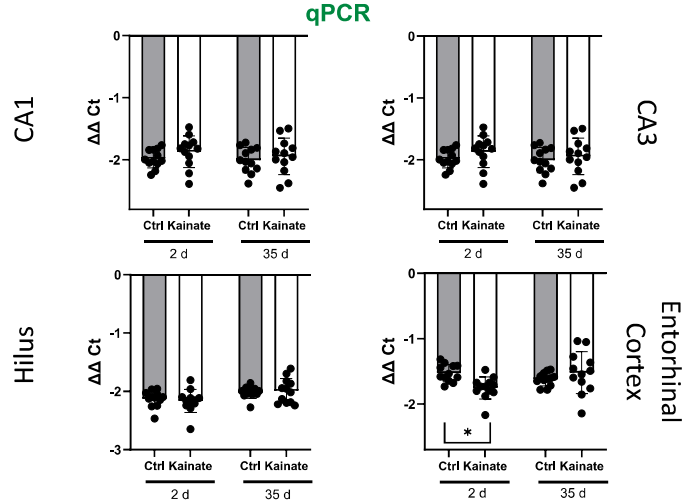
Stereological cell counting revealed consistent Sigma-1-positive cells per volume (mm^3) in the Entorhinal Cortex, CA1, CA3 region and Hilus of the Hippocampus across groups.

COLOCALIZATION



Colocalization analyses showed Sigma-1 expression in inhibitory (GAD67) and excitatory (vGlut1) neurons, in astroglia (GFAP) and in microglia (Iba1). Overview images: scale bar = 20 µm; detail images: scale bar = 5 µm.

qPCR



In the kainate model RNA levels in the CA1, CA3 region and Hilus of the Hippocampus did not differ from those of the control group. However, in the acute post-insult phase, there was a significant reduction in RNA levels in the Entorhinal Cortex.

CONCLUSION

In summary, the results indicate that Sigma-1 expression is preserved during epileptogenesis and after epilepsy manifestation, with only transient changes observed in the acute post-insult phase. This provides important information and a basis for considering it as a potential therapeutic target for epilepsy.

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