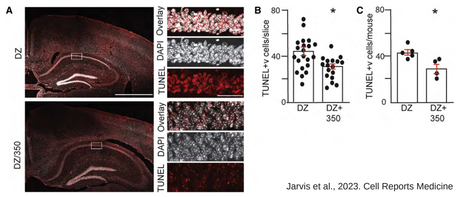
Potentiation of KCC2 shows neuroprotective and anti-inflammatory effects in kainic acid-induced refractory Status Epilepticus model

Toshiya Nishi[2], Shu Fun Josephine Ng[1], Aaron Goldman[2], and Stephen Moss[1,3].

[1]Department of Neuroscience, Tufts University School of Medicine, 136 Harrison Ave, Boston, MA 02111, United States. [2]Ovid Therapeutics, 1460 Broadway, New York, NY 10036, United States. [3]Department of Neuroscience, Physiology and Pharmacology, University College London, WC1 6BT, United Kingdom.

INTRODUCTION

- We descibed and reported the efficacy of OV350, a direct KCC2 activator, in reducing seizure severity, in limiting the development of benzodiazepine-resistant Status Epilepticus (BDZ-RSE) and in terminating ongoing BDZ-RSE. We also demonstrated that KCC2 activation by OV350 ameliorates neuronal cell death post-SE (Jarvis et al., 2023. Cell Reports Medicine).



Jarvis et al., 2023. Cell Reports Medicine

- Following up on our findings, we aim to:

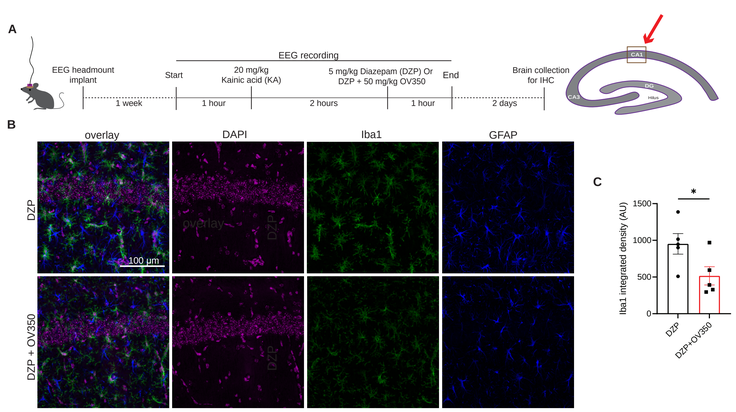
1. Examine the potential of KCC2 activation by OV350 (pharmacological intervention) in alleviating neuroinflammation and neuronal damage.

2. Investigate the efficacy of BDZ in suppressing RSE and in reducing neuroinflammation in a KCC2 phosphomutant knock-in mouse model, where KCC2 activity is enhanced.

3. Assess the effect of OV350 in abberant seizure-induced neurogenesis, which is associated with abnormalities in hippocampal circuitry.

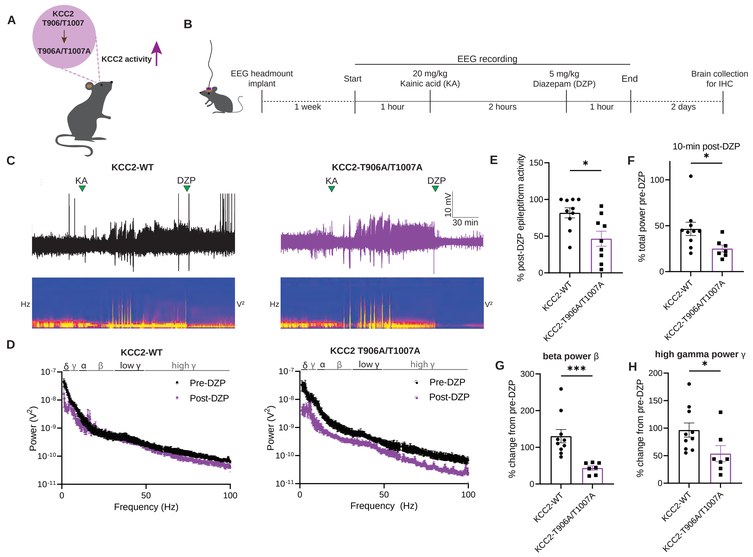
RESULTS

1. KCC2 activation by OV350 limits the neuroinflammation in animals, 48 hours post kainic acid-induced SE.



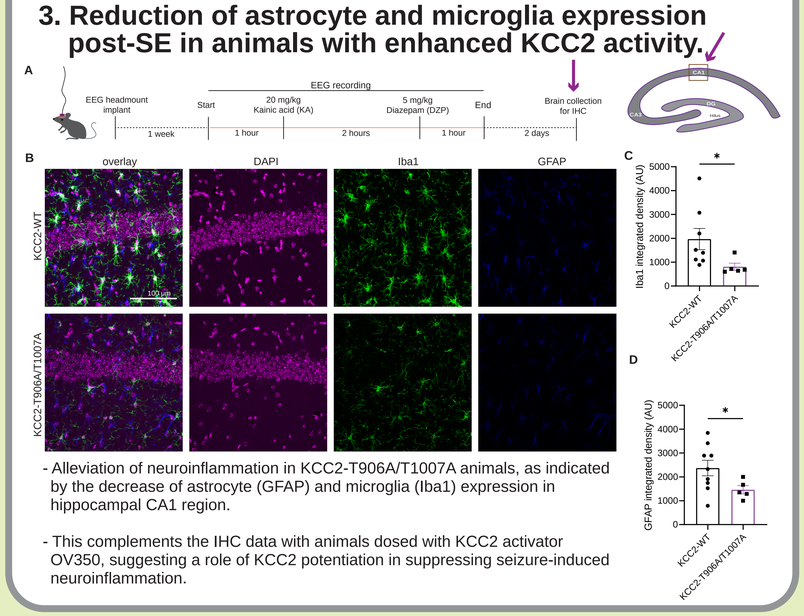
- In addition to a decrease in neuronal cell death, a reduction of neuroinflammation level was also observed in animals dosed with OV350, a KCC2 activator, 2 days after kainic acid induced-SE.

2. Diazepam (DZP) suppresses kainic-acid induced refractory SE in KCC2 phosphomutant T906A/T1007A knock-in mouse model.



- In KCC2-T906A/T1007A mutant model where KCC2 activity is enhanced, DZP is sufficient to suppress kainic acid-induced epileptiform activity and seizure power.

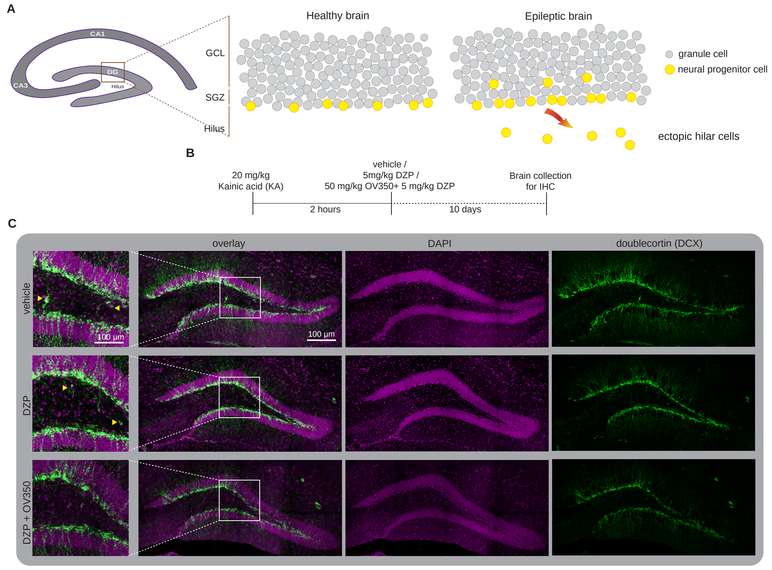
3. Reduction of astrocyte and microglia expression post-SE in animals with enhanced KCC2 activity.



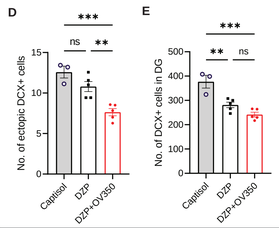
- Alleviation of neuroinflammation in KCC2-T906A/T1007A animals, as indicated by the decrease of astrocyte (GFAP) and microglia (Iba1) expression in hippocampal CA1 region.

- This complements the IHC data with animals dosed with KCC2 activator OV350, suggesting a role of KCC2 potentiation in suppressing seizure-induced neuroinflammation.

4. KCC2 activation reduces seizure-induced abberant neurogenesis and ectopic migration of granule cells in dentate gyrus



Yellow arrowhead indicates the ectopic neural progenitor cells in the hilus of the dentate gyrus.



- Ectopic migration of newborn neurons in the dentate gyrus is one of the hallmark features in animal models and human patients with epilepsy, which has implications in neuronal circuit dysfunction and hyperexcitability.

- Immunohistochemical staining of DCX (marker of neurogenesis) revealed a reduction of mislocated neural progenitor cells in the hilus in animals adminstered with OV350, a KCC2 activator.

SUMMARY

- Elevating KCC2 function by KCC2 activator OV350 attentuates the extent of seizure-induced neuroinflammation.

- In line with our findings with OV350, studies with the KCC2 phosphomutant model demonstrate that increase of KCC2 activity enhances the efficacy of BDZ to alleviate SE and help limit the subsequent neuroinflammation.

- KCC2 activation suppresses seizure-induced abberant neurogenesis and ectopic migration of neural progenitor cells in the hilus of dentate gyrus.

REFERENCES

1. Jarvis R, Josephine Ng SF, Nathanson AJ, Cardarelli RA, Abiraman K, Wade F, Evans-Strong A, Fernandez-Campa MP, Deeb TZ, Smalley JL, Jamier T, Gurrell IK, McWilliams L, Kawatkar A, Conway LC, Wang Q, Burli RW, Brandon NJ, Chessell IP, Goldman AJ, Maguire JL, Moss SJ. Direct activation of KCC2 arrests benzodiazepine refractory status epilepticus and limits the subsequent neuronal injury in mice. Cell Rep Med. 2023 Mar 21;4(3):100957.

2. Moore YE, Deeb TZ, Chadchankar H, Brandon NJ, Moss SJ. Potentiating KCC2 activity is sufficient to limit the onset and severity of seizures. Proc Natl Acad Sci U S A. 2018 Oct 2;115(40):10166-10171.