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Reduced efficacy of the KCC2 cotransporter promotes epileptic oscillations in a subiculum network model

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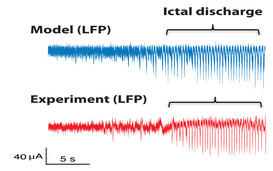
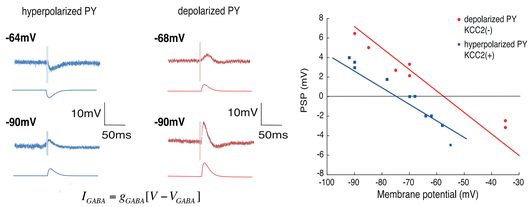
Introduction

- Ion regulation in the brain is a major determinant of neural excitability
- Intracellular chloride in neurons is regulated together with extracellular potassium by Kation Chloride Cotransporter 2 (KCC2)
- During temporal lobe epilepsy, the regulation of intracellular chloride is impaired in the pyramidal cells due to KCC2(-) pathology
- Using realistic neural network model describing ion mechanisms, we show that chloride homeostasis pathology provokes seizure activity
- We show that there is a crucial percentage of pathological cells required for seizure initiation
- Our model predicts that restoration of the chloride homeostasis in pyramdal cells could be viable aniepileptic strategy



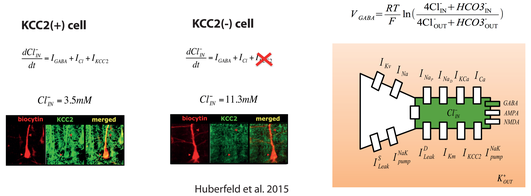
1 Absence of KCC2 leads to depolarizing GABA

Post-synaptic potentials induced by extracellular stimulation



$$I_{GABA} = g_{GABA}[V - V_{GABA}]$$

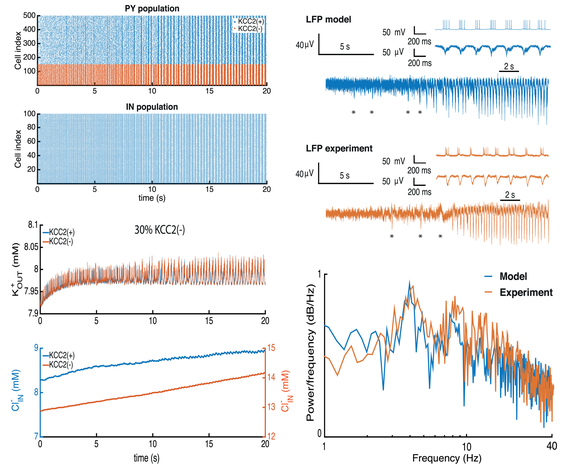
Mechanism of depolarizing GABA response



Huberfeld et al. 2015

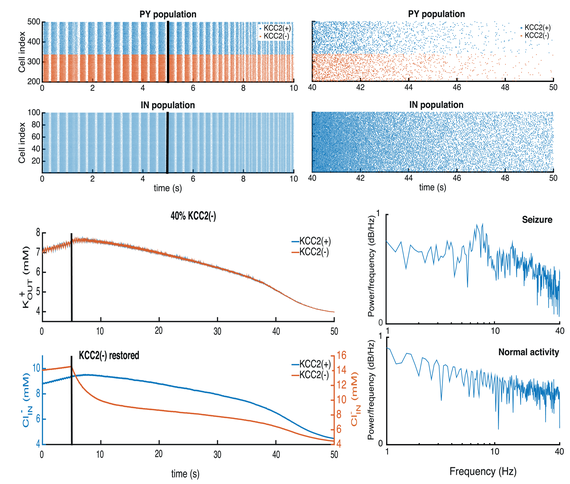
3 KCC2(-) pathology leads to epileptic oscillations

Transition to seizure due to chloride pathology



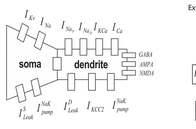
5 Restoring KCC2(-) function prevents seizure

The network restores the excitation-inhibition ballance after KCC2(-)

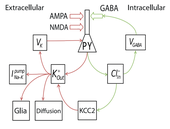


Model

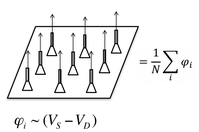
Single neuron



Krishnan et al. 2011

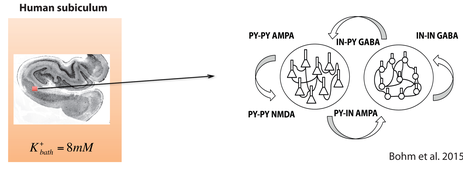


Local field potential



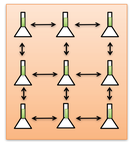
$$\varphi_i \sim (V_S - V_D)$$

Neural network



Bohm et al. 2015

Potassium diffusion



Ion dynamics

$$\frac{dCl^-_{IN}}{dt} = \frac{k_{Cl}}{F}(I_{GABA} + I^{Cl^-}_{Cl} - I_{KCC2})$$

$$I_{KCC2} = \frac{I^{max}_{KCC2}(V_K - V_{Cl})}{(V_K - V_{Cl}) + V_{1/2}}$$

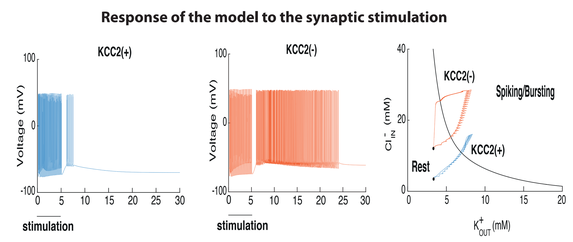
Doyon et al. 2011

$$\frac{\partial K^+_{OUT}}{\partial t} = R + \varepsilon\left(\frac{\partial^2 K^+_{OUT}}{\partial x^2} + \frac{\partial^2 K^+_{OUT}}{\partial y^2}\right) + \frac{\varepsilon_{bath}}{\Delta x^2}(K^+_{bath} - K^+_{OUT})$$

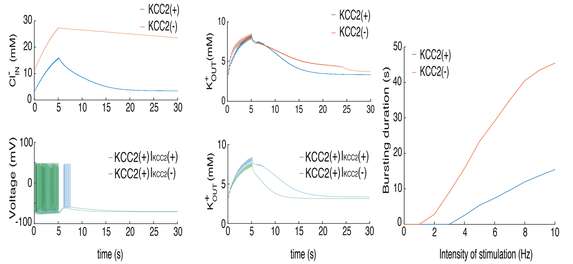
$$R = \frac{k_K}{Fd}(I_K + I^{NaK}_{pump} - I_{KCC2}) + G$$

2 KCC2(-) pathology increases excitability

Response of the model to the synaptic stimulation

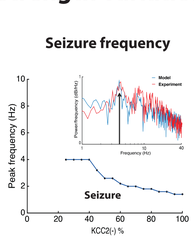


Ion concentration changes during stimulation

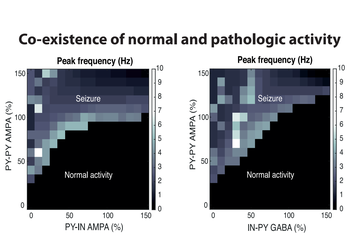


4 Epileptic oscillations are robust to synaptic strength variation

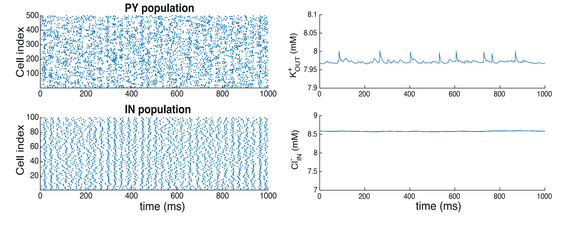
Seizure frequency



Co-existence of normal and pathologic activity

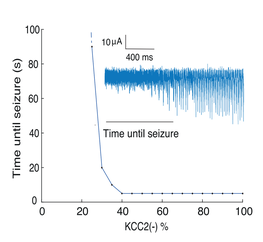


Ion dynamics during normal activity (gamma oscillations)



Conclusions

- KCC2(-) pathology leads to the depolarizing GABA reversal potential due to accumulation of intracellular chloride
- There is a critical amount of KCC2(-) pyramidal cells in the network required for seizure initiation
- Restoration of KCC2(-) function restores the excitation-inhibition balance



Related work

Buchin, Anatoly, et al. "Reduced efficacy of the KCC2 cotransporter promotes epileptic oscillations in a subiculum network model". The Journal of neuroscience. in press.

Krishnan, Giri P., and Maxim Bazhenov. "Ionic dynamics mediate spontaneous termination of seizures and postictal depression state." The Journal of Neuroscience 31.24 (2011): 8870-8882.

Huberfeld, Gilles, et al. "Perturbed chloride homeostasis and GABAergic signaling in human temporal lobe epilepsy." The Journal of neuroscience 27.37 (2007): 9866-9873.

Doyon, Nicolas, et al. "Efficacy of synaptic inhibition depends on multiple, dynamically interacting mechanisms implicated in chloride homeostasis." PLoS Comput Biol 7.9 (2011): e1002149.

Acknowledgements

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