Contribution of Delayed Rectifier to Dendrosomatic Signalling in Cerebellar Molecular Layer Interneurons

Nils A Koch [1,2] ✉, Arjun A Bhaskaran [2,3], Erik A Larson [3], Derek Bowie [3], and Anmar Khadra [1]

[1]Department of Physiology, McGill University, Montréal, QC, Canada
[2]Integrated Program in Neuroscience, McGill University, Montréal, Québec, Canada
[3]Department of Pharmacology and Therapeutics, McGill University, Montréal, QC, Canada

✉nils.koch@mail.mcgill.ca

Introduction: Cerebellar Stellate Cells and Fragile X Syndrome

- **Cerebellar stellate cells** (CSC)
  - **Inhibitory** molecular layer **interneurons**
  - Synapse onto Purkinje cells and other CSC
  - Receive **glutamatergic parallel fiber** and **CSC GABAergic synaptic inputs**
- **Fragile X Syndrome** (FXS)
  - Genetic disorder associated with **intellectual disability**
  - Generally associated with **neuronal hyperexcitability** and **altered synaptic transmission** in CSC (EPSP and IPSP)
  - Knockout model (Fmr1-/-) CSC **do not show EPSP potentiation with TEA**

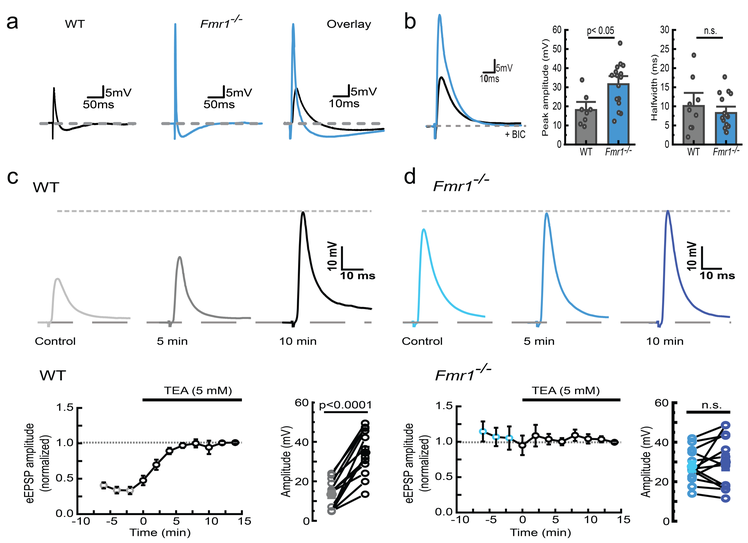

Figure 1: Larger and briefer TEA insensitive EPSP waveform in Fmr1-/- cerebellar stellate cells. (a) Representative eEPSP recordings from a WT (left), and Fmr1-/-(center) CSC in current-clamp mode. The traces are then overlaid (right) to compare the differences in their properties. QX-314 was included in the patch pipette to block NaV and action potential firing. (b) Representative EPSP recordings (overlaid) from a WT and Fmr1-/- CSC in current-clamp mode. QX-314 was included in the patch pipette to block NaV and action potential firing. Bicuculline was included in the aCSF throughout the experiment to prevent GABAergic currents. Summary plots comparing the overall depolarization amplitude and half-width of the eEPSP waveforms. Representative eEPSP recordings from (c) a WT and (d) an Fmr1-/- CSC at baseline (control), 5 mins, and 10 mins after washing in of 5 mM TEA-Cl. QX-314 was added to the internal solution to block Nav channels and action potential firing. Summary plot of the average eEPSP amplitude change over time during wash in of 5 mM TEA-Cl in WT CSCs (c, bottom left) and in in Fmr1-/- CSCs (d, bottom left). Summary plots representing the eEPSC amplitude before and, after 10 mins of application of 5mM TEA-Cl in WT (c, bottom right)and Fmr1-/- CSCs (d, bottom right). (Error bars, s.e.m).

- **Computational modelling**: evaluate which neuronal properties may underlie the difference between Wt and Fmr1-/- CSC EPSP responses to TEA as well as Fmr1-/- CSC hyperexcitability

Cerebellar Stellate Cell Model

2 compartment Hodgkin-Huxley type model: somatic and dendritic compartments

$$\begin{cases} C\dot{V}_s = I_{app} - I_{Na,s} - I_{Kdr,s} - I_{L,s} - I_{A,s} - I_{T,s} - I_{K(Ca),s} - I_{HVA,s} - \frac{g_c}{\kappa}(V_s - V_d) \\ C\dot{V}_d = I_{app} - I_{Kdr,d} - I_{L,d} - I_{A,d} - I_{T,d} - I_{K(Ca),d} - I_{HVA,d} - \frac{g_c}{1-\kappa}(V_d - V_s) - I_{syn} \\ \dot{x}_\theta = \frac{x_{\infty,\theta} - x_\theta}{\tau_x}, \qquad x = h, n, n_A, h_A, h_T, m_{HVA} \qquad \theta = s, d \\ \dot{Ca}_s = -\varepsilon\left(\alpha\left(I_{T,s} + I_{HVA,s}\right) + kCa_s\right) \\ \dot{Ca}_d = -\varepsilon\left(\alpha\left(I_{T,d} + I_{HVA,d} + fI_{syn}\right) + kCa_d\right). \end{cases} \quad (1)$$

Excitatory Synaptic Input

$$I_{syn} = g_e H\left(t - t_{syn}\right)\left[exp\left(-\tau_{e,d}\left(t - t_{syn}\right)\right) - exp\left(-\tau_{e,r}\left(t - t_{syn}\right)\right)\right] \quad (2)$$

Effects of K+ Currents on Cerebellar Stellate Cell EPSPs

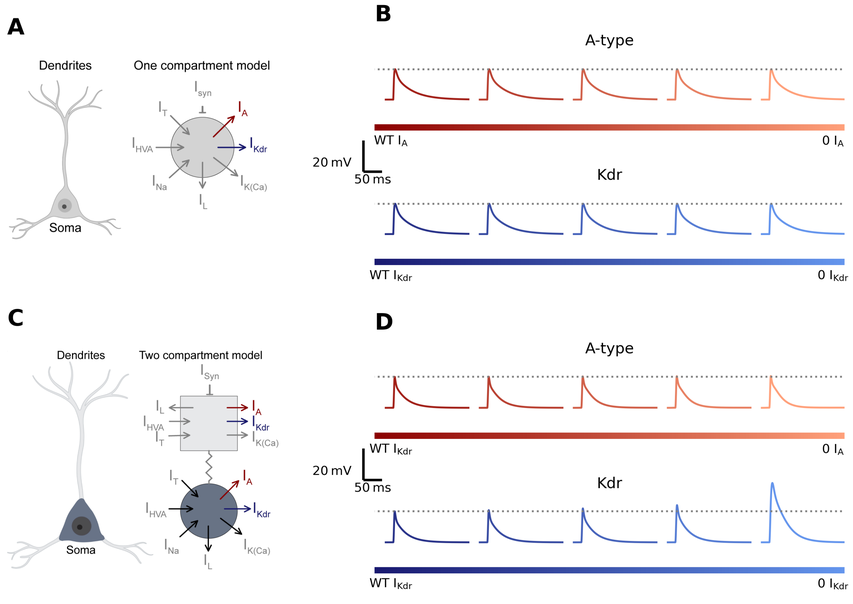

Figure 2: Delayed rectifiers contribute AMPAR mediated glutamatergic signaling in Cerebellar SCs. (A) Schematic showing one compartment model (uniform colour of neuron (A, left) implicate the model consider the entire neuron as one compartment). (B) The effects of scaling the A-type potassium current (I_A), and delayed rectifier potassium current (I_{Kdr}) from no current (0 I_A or I_{Kdr}) to the default model value (WT I_A or I_{Kdr}) on EPSP amplitude were simulated in a 1 compartment SC model. (C) Schematic representation of two compartment model (C, right) and corresponding colour coded native neuron. Dendrites in light grey and the soma in dark grey (C, left). The A-type and Kdr currents are scaled in a two-compartment SC model in both somatic and dendritic compartments.

- Delayed rectifier but not A-type K+ Currents determine CSC EPSP amplitudes

Somatic and Dendritic Delayed Rectifier Currents Determine CSC EPSP Waveforms

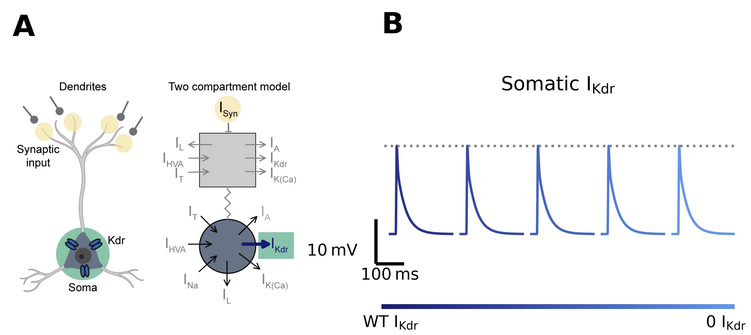

Figure 3: Dendritic delayed rectifiers exclusively regulate AMPAR mediated glutamatergic signaling in Cerebellar SCs. (A) and (C) Schematic representation of two compartment model (right) and corresponding colour coded native neuron. Dendrites in light grey and the soma in dark grey. Changes to Kdrs in soma (A) and dendrites (C) are indicated in green. The effect of scaling Kdr currents in a two compartment SC model in somatic compartment only (B) or in dendritic compartment only (D). In the absence of dendritic Kdr current, scaling the somatic Kdr current alters EPSP shape (E).

- Spatial current distribution is vital to reproduce experimental increases in EPSP amplitude
- Decreased dendritic delayed rectifier K+ results in increased EPSP amplitude

Dendritic Delayed Rectifier K+ Currents Regulate Excitability

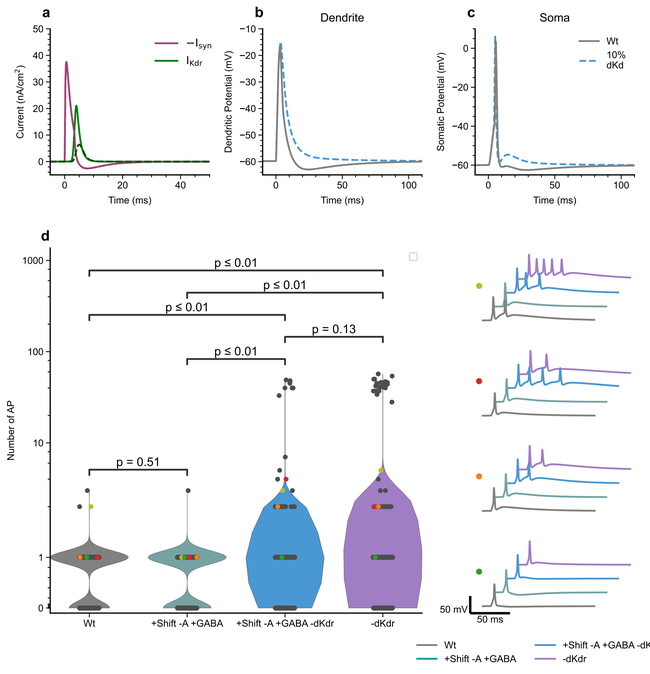

Figure 4: Computational modelling of the impact of dendritic delayed rectifier potassium currents on cerebellar stellate cell firing. The synaptic current (I_{syn}) and delayed rectifier current (I_{Kd} in the dendritic compartment of a two compartment CSC model are shown for wild type condition and with 10% dendritic level of delayed rectifiers (a) for the biphasic response. The corresponding changes in dendritic (b) and somatic (c) potentials for wild type and for 10% dendritic delayed rectifier conditions are shown. The number of action potentials (AP) fired for 1000 heterogeneous CSC models is increased with FXS-like shifts in I_{Kd} activation, decreased I_A and increased GABAergic synaptic input with 10% dendritic delayed rectifier (+Shift -A +GABA -dKdr) compared to wild type (Wt) and FXS-like shifts in I_{Kd} activation, decreased I_A, and increased GABAergic IPSP amplitude (+Shift -A +GABA) conditions (d). Traces from 4 cells highlighted in color are shown on the right for the 3 conditions. CSC models were generated random sampling and modification of the following model parameters:
$g_{A,\theta} * X_{A,\theta} \sim \mathcal{N}(1, 0.2)$,
$g_{HVA,\theta} * X_{HVA,\theta} \sim \mathcal{N}(2, 0.75)$,
$g_{T,\theta} * X_{T,\theta} \sim \mathcal{N}(1.5, 0.5)$,
$I_{syn} * X_{syn} \sim \mathcal{N}(1, 0.2)$,
$\tau_{e,r} * X_{e,r} \sim \mathcal{N}(1., 0.2)$,
$\tau_{e,d} * X_{e,d} \sim \mathcal{N}(1., 0.2)$,
$\tau_{i,r} * X_{i,r} \sim \mathcal{N}(1., 0.2)$
$\tau_{i,d} * X_{i,d} \sim \mathcal{N}(1., 0.2)$,
$t_\delta * X_\delta \sim \mathcal{N}(1., 0.2)$,
$f * X_f \sim \mathcal{N}(1., 0.2)$,
$g_i * X_i \sim \mathcal{N}(2., 0.75)$.

- Dendritic delayed rectifier decreases increase CSC AP firing with heterogeneity across cells

Conclusions

- **Dendritic I_{Kdr}** regulates **CSC excitability** and **dendrosomatic AMPA receptor signalling**
- Fragile X Syndrome: **Decreased dendritic I_{Kdr}** contributes to **increased EPSP amplitude** and **hyperexcitability**
- Understanding **dendritic filtering and integration** is **key** to understanding **hyperexcitability in Fragile X Syndrome** at the cellular and network levels

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