Modeling mGluR1 mediated synaptic depression in cerebellar Purkinje cells

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INTRODUCTION

The cerebellar cortical output to the deep cerebellar nuclei is via the Purkinje cell axon. The plasticity of the Purkinje cell synapses is determined by the mossy fiber and climbing fiber inputs (Fig. 1). The mGluR1 channels are known to participate in Purkinje cell plasticity. In our previous study, we have successfully simulated mGluR1 mediated sEPSP based on experimental data [1]. It is known that this mGluR1 mediated response is associated with parallel fiber – Purkinje cell LTD [2, 3]. Recent studies have shown that the mGluR1 mediated sEPSP is generated by calcium signaling through the TRPC channel and this channel is crucial in cerebellar LTD induction [4]. Behavior study using mutant mice that lack this type of LTD has shown no motor learning impairment [5]. If cerebellar LTD is not essential for motor learning, what is the function of synaptic depression in Purkinje cells? Due to the fact that neuronal activity can also modulate mGluR1 function, we hypothesize that cerebellar TRPC mediated synaptic depression shifts the excitatory and inhibitory balance to down regulate ongoing simple-spike activity. To test our hypothesis we modified our previous model of a Purkinje cell [1] based the simulation script SYNCHRONORM9.g[6, 7]. We have the TRPC channel current signal linked to the AMPA channel conductance through Kinetikit [8].

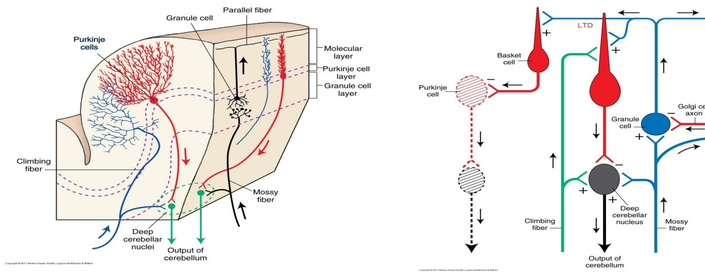

Figure 1 Basic circuitry of cerebellar cortex. (modified from Siegel and Sapru, *Essential Neuroscience 2nd ed.*, Figure 21.8 and Figure 2.10)

METHODS

Genesis 2.3 [9] was used to simulate the mGluR1 mediated plasticity. The model was implemented using two distinct steps. The first step involved modeling a local model including one dendritic segment, a spine neck, and a spine head (Fig. 2A). Since the TRPC current inducted cerebellar LTD is not associated with changes in AMPA-receptor kinetics [10], we simulated the depression effects by linking the TRPC current (I_k) directly to the AMPA-receptor density (g_{max}) change before (g_{max_old}) and after (g_{max_new}) the stimulation using the following:

$$g_{max\_new} = g_{max\_old}\left(1 - 0.4\left(\frac{Ik}{Ik\ max}\right)\right)$$

Where the value of 0.4 is the maximum change in percentage of the EPSC after the induction of cerebellar LTD [4]. The g_{max} in Genesis is normally a constant in simulation as shown:

$$I_{TRPC} = g_{max} \bullet f(v) \bullet g([TRPC1^*]) \bullet (V - E_{rev})$$

Where g_{max} is a constant, *f(v)* is the voltage activation of the channel, *g([TRPC1*])* is a function describing the activation of the Gq-bound TRPC1 channels (range 0-1), *V* is the compartment voltage, and E_{rev} is the reversal potential.

To make it variable as the consequence of I_k change, we used a script_out object to generate a g_{max_new} for every time step. In the second step, the local model was applied to the whole Purkinje cell dendritic tree using the existing model [6, 7; Fig. 2B]. Simple spike data was analyzed using MATLAB (2013a, Mathworks).

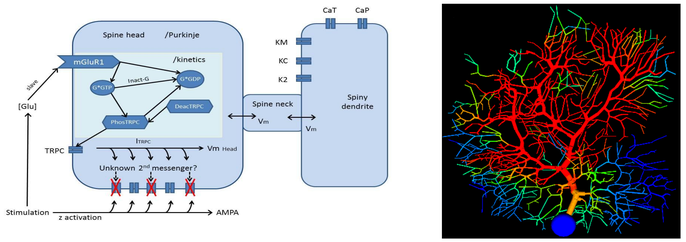

Figure 2. **A.** Local model constructed to simulate fEPSP depression triggered by TRPC channel current. Local model is constructed using three compartments: head, neck and dendrite. TRPC channel current (Ik) increase due to activation of mGluR1 is linked to AMPA channel conductance (gmax) to simulate the decrease of the channel density. **B.** Full model of Purkinje Cell [7, 8]

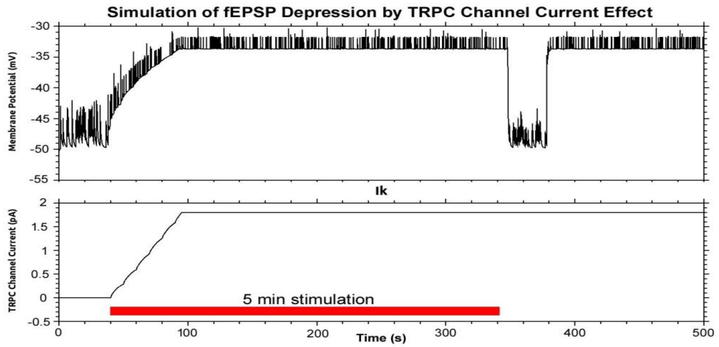

Figure 3 Local model constructed to simulate fEPSP depression triggered by TRPC channel current.

fEPSPs are evoked randomly at 1 Hz to monitor the amplitude change of the depression effect caused by TRPC current (Ik). After 5 min train stimulation (10 pulses at 100 Hz, 1 stimulation / s) through mGluR receptors, membrane potential is adjusted to the same level as before the stimulation using a current injection (-2.25 pA) for comparison.

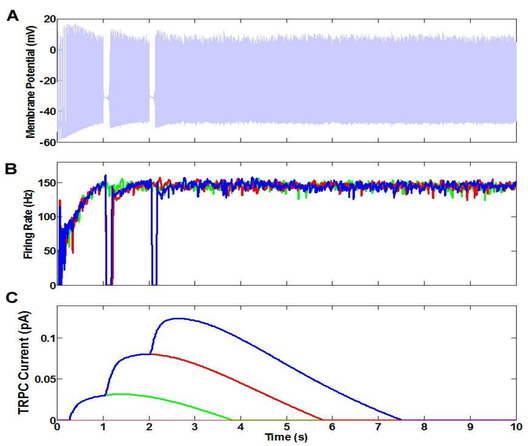

Figure 4. Firing rate change by individual train stimulation through mGluR1 mediated TRPC currents.

A. Pukinje cell soma potential to show the spiking pattern change by three train stimulations (0, 1, and 2 s). **B.** Purkinje cell firing rate change with 1, 2 and 3 train stimulations (green, red and blue). Notice that Purkinje cell stopped firing when each train stimulation is delivered which is also aligned with the rising phase of the TRPC current (**C**) recorded from one spine.

As shown in Fig. 4, each train stimulation delivered through Purkinje cell spines is able to cause a pause in firing. The pulse has a 200 ms duration which is just the length of the train stimulations. During this time, it is also the rising part of the TRPC current. When the current reached the peak, the firing rate returned to its baseline.

To test if TRPC mediated synaptic depression is capable of regulating the firing rate by shifting the excitatory and inhibitory balance, we gave 3 train stimulations with the background randomized input in different combinations from following: excitatory - 15, 30 and 60 Hz; inhibitory - 0.5, 1, 1.5 and 2 Hz. We found that the effects of TRPC current is very transient since its link to the AMPA channel gmax is direct. When inhibition is relative strong, the train stimulation will cause the Purkinje cell to fire few spikes then return to baseline. When excitatory input is relative strong, bursting firing pattern can be seen, but that is unlikely due to the mGluR1 effect through TRPC channels.

RESULTS

The local model was used to test the depression effect of TRPC current onto the AMPA receptors. A train stimulation (10 pulses at 100 Hz) was delivered to the head compartment every 1 second for 5 min. This stimulation paradigm was used by the *in vitro* experiments to generate LTD. TRPC current (Ik) reached maxium (1.8 pA) after 7 train stimulations (Fig. 3). The sEPSP generated by this stimulation lasted 6 minutes at -34 mV (from -49 mV, bottom panel in Fig. 3) before it shifted to -35 mV. The membrane potential was maintained at this level till the end of the simulation (30 min). TRPC current stayed at 1.5 pA level while the membrane potential was in the decay phase of the sEPSP. To compare the change on fast EPSPs (fEPSPs) due to the TRPC current, after 5 min stimulation, we injected current (-2.25 pA) into the dendritic compartment to bring the membrane potential down to the same level as the initial state. The amplitude of those fEPSPs were reduced clearly (Fig. 3).

From the local model, we also learned that 3 train stimulations can generate 50% of the maximum TRPC current in the head compartment. Therefore, the first simulation using the full model was to test the firing rate change by individual train stimulations. The randomized background input was set at 28 Hz for excitatory and 1 Hz for inhibitory.

CONCLUSION

The synaptic depression mediated by TRPC channel current is successfully simulated in the local model. With a time delay, this model can be used to study real time LTD occurred at Purkinje cell spines. Synchronized train stimulation to the spines in the full model of Purkinje cell were able to cause the cell to fire then followed by a gap in spiking. This was caused by the reduction in g_{max} of AMPA channels, so the existing inhibition hyperpolarized the cell. Once the TRPC current passed the rising phase, the firing resumed. This model will be used to guide the *in vitro* experiments to study the interaction of TRPC current mediated depression with simple spike activities. Once the second messenger(s) and the delay time of the plastic effects are know, this model can be further used to study the function of cerebellar LTD.

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