

# Contribution of Somatic and Dendritic SK Channels in the Firing Rate of Deep Cerebellar Nuclei: Implication in Cerebellar Ataxia

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## ABSTRACT

**Introduction:** Loss of inhibitory output from Purkinje cells leads to hyperexcitability of the Deep Cerebellar Nuclei (DCN), which results in cerebellar ataxia. Also, inhibition of small-conductance calcium-activated potassium (SK) channel increases firing rate of DCN, which could cause cerebellar ataxia. Therefore, SK channel activators can be effective in reducing the symptoms of this disease, and used for the treatment of cerebellar ataxia. In this regard, we hypothesized that blockade of SK channels in different compartments of DCN would increase firing rate with different value. The location of these channels has different effects on increasing firing rate.

**Methods:** In this study, multi-compartment computational model of DCN was used. This computational stimulation allowed us to study the changes in the firing activity of DCN neuron without concerns about interfering parameters in the experiment.

**Results:** The simulation results demonstrated that blockade of somatic and dendritic SK channel increased the firing rate of DCN. In addition, after hyperpolarization (AHP) amplitude increased with blocking SK channel, and its regularity and resting potential changed. However, action potentials amplitude and duration had no significant changes. The simulation results illustrated a more significant contribution of SK channels on the dendritic tree to the DCN firing rate. SK channels in the proximal dendrites have more impact on firing rate compared to distal dendrites.

**Discussion:** Therefore, inhibition of SK channel in DCN can cause cerebellar ataxia, and SK channel openers can have a therapeutic effect on cerebellar ataxia. In addition, the location of SK channels could be important in therapeutic goals. Dendritic SK channels can be a more effective target compared to somatic SK channels.

## 1. Introduction

Cerebellum coordinates movement and helps maintain balance and posture. Its three deep nuclei provide the main output of the cerebellum. These neurons receive inhibitory inputs from cerebellar Purkinje cells, and excitatory collaterals from mossy and climbing fibers (Alviña & Khodakhah, 2008).

Cerebellar ataxia is a disease defined by disturbance in coordination, postural instability, gait abnormalities, and intention tremor, which has many molecular causes (Grüsser-Cornehls & Bäurle, 2001; Janahmadi et al., 2009; Shakkottai et al., 2004). It is generally believed that, ataxia is caused by cerebellar cortical degeneration. Irrespective of the nature of the cerebellar cortical defect, this disease is the result of changes in the output of cerebellar Purkinje cells. Malfunction of Purkinje neurons would be expected to enhance DCN hyperexcitability. DCN neurons project to motor centers in the nervous

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system, and enhanced DCN excitability might affect motor performance at multiple levels (Shakkottai et al., 2004). Disrupting their activity would result in severe cerebellar ataxia (Alviña & Khodakhah, 2008).

Most of experimental studies on animal models of cerebellar ataxia exhibit cerebellar cortical degeneration (Grüsser-Cornehls & Bäurle, 2001). Nevertheless, Shakkottai et al. (2004) reported that ataxia could be produced without disturbance of Purkinje cells output. They observed ataxia in transgenic (Tg) mice, which expressed SK3-1B protein in DCN. This protein is Small-conductance Calcium-activated Potassium (SK) channels inhibitor. In many neurons, SK channels play a fundamental role in the cell firing by contributing to a slow after hyperpolarization and mediating spike frequency adaptation (Bond, Maylie, & Adelman, 1999; Womack & Khodakhah, 2003). There is some evidence to suggest that these channels may play a crucial role in the cerebellum (Kaffashian et al., 2011; Shakkottai, et al., 2004; Womack & Khodakhah, 2003). Inactivation of these channels increases DCN firing rate. The direct relationship between increased DCN firing rate and ataxia was demonstrated (Orr, 2004; Shakkottai et al., 2004). Therefore, enhancement in DCN firing rate can be due to impaired Purkinje cells function, change in the construction of DCN proteins, or ion channels.

Shakkottai et al. (2004) showed that observed alternations in DCN firing rate in the SK3-1B mice happened in the lack of any apprehensible changes in several other electrical parameters of DCN neurons. They also demonstrated that changes in DCN firing rate took place in the absence of any symptoms of pathology or degeneration

in the cerebellar cortex or elsewhere in the brain (Orr, 2004).

An experimental study (Schneider, 2012) suggested that DCN neurons have active dendrites capable of processing separately from the soma. This study also investigated T-type calcium channels in distal and proximal dendrites. However, it is more convenient to do this by computer simulation. So, we investigated the role of SK channels blockade in soma, distal dendrites, proximal dendrites, and whole dendrites by using computer simulation. Computer simulations of a morphologically realistic model of DCN neuron have been applied to compare the effects of somatic and dendritic SK channel in the firing rate of this neuron. The simulation approach used in the present study allowed the assessment of location dependence of SK channels in the firing rate of DCN neuron, and could be used to compare the location dependence of voltage-gated currents. The results of this study could determine which SK channels (somatic or dendritic) should be the target of neuroprotective agents. So, these results could help in the treatment of cerebellar ataxia.

## 2. Methods

In this simulation study, multi-compartmental conductance-based model of DCN neuron has been used (Luthman et al., 2011). Luthman et al. provided this computational model to simulate firing activity of DCN. The model contains 517 compartments (soma: 1 compartment, axon hillock: 1 compartment, axon initial segment: 10 compartments, axon node: 20 compartments, proximal dendrites: 83 compartments, and distal dendrites: 402 compartments) along with 10 ion channel mechanisms that were represented by using Hodgkin-

**Table 1.** Channel mechanisms and conductance densities in S/m<sup>2</sup> (and for CaHVA and CaLVA permeability in m/s) for the different compartment types. In the Table, axon refers to the conductance densities in the axon hillock and initial segment [10].

Current	NaF	NaP	fKdr	sKdr	CaHVA	CaLVA	h	SK	TNC	Pas
Gating	m <sup>3</sup> h	m <sup>3</sup> h	m <sup>4</sup>	m <sup>4</sup>	m <sup>3</sup>	m <sup>3</sup> h	m <sup>2</sup>	Ca con	none	none
Soma	250	8	150	125	7.5e-8	1.77e-7	2	2.2	0.3	28.1
Proximal dend	100	0	90	75	5e-8	3.54e-7	4	0.66	0.06	28.1
Distal dend	0	0	0	0	5e-8	3.54e-7	6	0.66	0	28.1
Axon	500	0	300	250	0	0	0	0	0.35	1

NaF: Fast sodium current

NaP: Persistent sodium current

fKdr: Fast delayed rectifier (potassium current)

sKdr: Slow delayed rectifier (potassium current)

CaHVA: High voltage-activated calcium current

CaLVA: Low voltage-activated calcium current

SK: Small-conductance calcium-activated current

TNC: Tonic non-specific cation

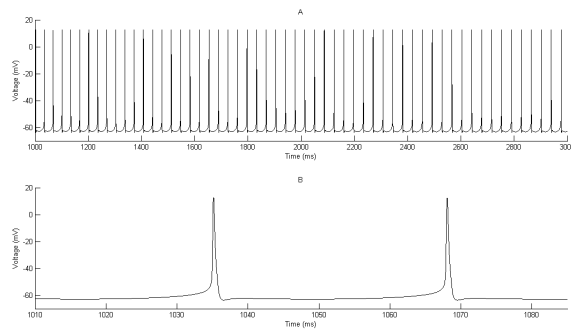
Ca con: Calcium concentration

h: h current

Pas: Passive current

dend: dendrite

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**Figure 1** A. Membrane potential at the soma for two seconds. B. The shape of the two spikes from DCN model.

Huxley model. These ion channel mechanisms and conductance densities are listed in Table 1. The first 7 mechanisms in Table 1 are voltage gated channels, followed by SK channel and the 2 passive currents (Luthman, J., 2012; Luthman et al., 2011). The gating expressions correspond to  $m^a h^b$  in the Hodgkin-Huxley model. In this model the conductance  $g$  of a voltage-gated channel is presented by the following equation.

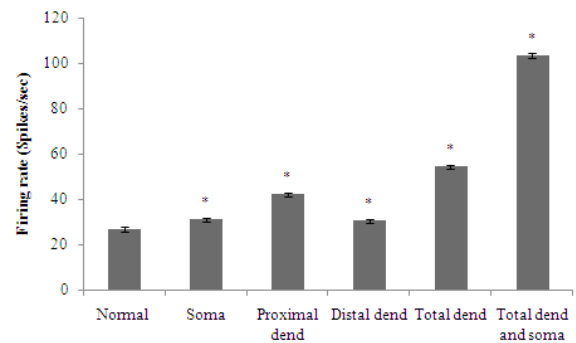
$$g = g_{\max} m^a h^b \quad (1)$$

Where  $g_{\max}$  denotes the maximum conductance of the channel,  $m$  and  $h$  are the activation and inactivation variables, respectively. Constants  $a$  and  $b$  are exponents of the activation and inactivation variables, respectively.

The intracellular calcium concentration was modeled as a submembrane shell with calcium inflow from high voltage-activated current and an exponential decay with a time constant of 70 ms (Luthman et al., 2011).

This model could fire spontaneously in the absence of synaptic inputs, also in the presence of synaptic inputs. Excitatory input from 150 mossy fiber synapses was added to the model, 100 of which were located at 100 randomly chosen dendritic compartments, and the remaining 50 synapses added to the soma. The inhibitory input was modeled as 450 Purkinje cell synapses, one for each of 400 randomly chosen dendritic compartments and 50 situated on the soma. The reversal potential of the excitatory synaptic current was set to 0 mV, and  $-75$  mV for inhibitory current. The means of activation rate of excitatory and inhibitory inputs were set to 20 and 40 Hz, respectively.

To investigate the firing activity of the neuron in the presence of ion channel inhibitor, the maximum conductance of ion channel was set to zero in different compartment of the model, and its effect on firing activity of the DCN was stud-



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**Figure 2.** Firing rates of DCN with blockade of SK channel in each compartment. ‘\*’ denote significant differences between normal conditions, blockade of SK channel in soma, and in soma along with dendrites ( $P=0.8e-4$ ).

ied. The simulations were performed in the NEURON (Version 7.1) (Hines & Carnevale, 1997), and run with a time step of 25  $\mu$ s. Simulation data were analyzed using MATLAB. The firing activity of the simulated neurons was assessed in 20-s interval. The results were expressed as mean  $\pm$  standard deviation (SD). Statistical analyses were performed by Wilcoxon signed-rank test, and differences were considered significant if  $P < 0.05$ .

### 3. Results

Simulation of DCN neuron demonstrated firing at  $26.6 \pm 0.5$  spike/s, while an initial membrane potential was about  $-62.72$  mV (Figure 1). These results are consistent with the measurements of the firing activity of DCN in the reference model as reported by Luthman et al. (2011); so these results are validated.

In order to simulate the effect of SK channels blocker, the conductance of this channel was set to 0 in different compartments of DCN model. Simulations indicated that blockade of SK channel increased the firing rate of DCN. When SK channel was blocked in different compartments such as soma, proximal dendrites, distal dendrites, total dendrites, and soma along with dendrites, we observed increase in firing rate. When SK channel in soma was blocked, DCN fired in  $30.9 \pm 0.9$  spike/s. Blocking of proximal and distal dendritic SK channels alone increased the firing rates to  $42.1 \pm 0.9$  and  $30.4 \pm 0.7$  spike/s, respectively. With inhibition of SK channel in all dendrites, and soma along with all dendrites, enhancement in firing rate got more remarkable, and increased to  $54.2 \pm 1.3$  and  $103.4 \pm 1.9$ , respectively (Figure 2).

The mean and standard deviation of Inter-spike Intervals (ISIs) between spikes were calculated, and for the evaluation of the firing regularity, the coefficient of variation (CV) was calculated from the ratio of SD to mean ISI. With the block-

**Table 2.** Electrophysiological characteristics of DCN neuron before and after the blockade of SK channel. First row indicates the compartment that SK channel was blocked in.

	Normal	Soma	Proximal dend	Distal dend	Total dend	Total dend and soma
Resting Potential (mV)	-62.72	-62.21	-61.87	-62.41	-61.44	-60.45
CV of ISIs Mean±SD	0.0047± 0.0097	0.0068±0.0153	0.0051±0.0104	0.0056±0.0110	0.0058±0.0113	0.0048±0.0074
AHP (mV) Mean	0.96	1.47	1.89	1.31	2.4	3.37

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ade of SK channel, coefficient of variation of inter-spike interval increased so the firing of DCN neurons was more irregular with respect to normal conditions.

AHP amplitude had remarkable changes in the conditions of blocking SK channel in different compartments. According to Table 2, AHP has a direct relationship with the firing rate. However, the mean amplitude of action potentials (APs) and duration were about 75 mV and 0.4120 ms, respectively. These parameters had no considerable alternations with blockade of SK channels. Results are summarized in Table 2.

#### 4. Discussion

Cerebral cortical degeneration is a sign of cerebellar ataxia and this degeneration leads to alternation in Purkinje cells output. Purkinje cells are the sole output source of cerebellar cortex and send inhibitory project to DCN (Farley, 2004). DCN neurons exhibit spontaneous firing even in the lack of synaptic input from PCs, and it is deemed that modulation of the DCN firing response by Purkinje input is responsible for coordination of movement. Impaired performance of Purkinje cells results in enhancement of the firing rate of DCN. Intrinsic DCN hyperexcitability has been shown to inure ataxia in the lack of upstream Purkinje degeneration in the transgenic (Tg) mice model that protects this mechanism of disease (Shakkottai et al., 2004). SK channels were silenced in the DCN of Tg mice. This mechanism indicated that intrinsic DCN hyperexcitability causes ataxia in the absence of upstream Purkinje degeneration (Farley, 2004; Shakkottai et al., 2004).

Thus, SK channel openers may have a beneficial effect on cerebellar ataxia. Experimental studies showed that administration of an activator of SK channels, partially corrected abnormal DCN firing and improved motor function (Farley, 2004; Walter, Alvina, Womack, Chevez, & Khodakhah, 2006). Since, dendrites are an ideal site for studying molecu-

lar mechanisms of channel targeting (Yuan & Chen, 2006) and DCN neurons have active dendrites (Schneider, 2012); we investigated the effect of inhibition of dendritic and somatic SK channels in the firing rate of DCN by computer simulation.

Computational models could help predict results and the predictions in turn could be tested by actual experiments. In this way, the impact of dendritic conductance, alone or in combination with other ion channels, can be studied in greater detail (Abbasi, Edrisi, Mahnam, & Janahmadi, 2013). Also, the effects of different ion current mechanisms in the firing patterns of neuron could be investigated in simulations (Daneshparvar & Daliri, 2012). Therefore, we used a computer simulations approach to examine the effects of somatic and dendritic SK channel in the firing of a DCN neuron. This approach allowed us to compare the effect of blockade of SK channel in different parts with regard to the firing rate of DCN neuron. By this method, we were able to find differences in the firing rate of this neuron when SK channels in different compartments were inhibited. This study revealed the impact of location of SK channel in the firing rate. These results are helpful in finding treatment that can help ataxic patients leading to normal life. These treatments can be neuroprotective agents that target the ion channels such as SK channel.

Simulation results indicated that inhibition of SK channels enhanced firing rate of DCN. These results were consistent with experimental observations (Shakkottai et al., 2004) that reported increased firing activity, when SK channel was blocked with apamin, a specific SK channel blocker, also in Tg mice. It was reported that normal DCN neurons fire at approximately 6.3 Hz and DCN neurons exposed to 100 nM apamin fire more rapidly at approximately 15.2 Hz also Tg DCN fire at approximately 16.6 Hz (Shakkottai et al., 2004).

Our simulation results showed that DCN firing activity is more irregular in the condition of somatic SK channel block-

ade. This result is consistent with the experimental results that reported blockade of SK channel increased CV in firing activity of some cells (Rouchet et al., 2008). Also, our results indicated that blockade of distal dendritic SK channel had less effect on the firing rate of DCN; however, blockade of total dendritic SK channel had more effect on the firing rate with respect to the somatic SK channel.

The location and properties of ion channels therefore play critical roles in the activity of the neuron, which is the foundation for more complex computations at network levels (Yuan & Chen, 2006). In summary, simulation results indicate that blockade of SK channels in different compartments of DCN neuron increases firing rate; this hyperexcitability causes cerebellar ataxia. The location of these channels has different effect on increasing firing rate. This block is more effective at proximal sites than distal dendrites. The results from this study suggested that SK channel openers can help reduce the symptoms of cerebellar ataxia and be used as a therapy for cerebellar ataxia.

### Conflict of interest

None declared.

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