

Single-Cell Model of Orexin Neuron and Adaptive Glucose-sensing Mechanism

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Abstract. Orexin neurons are critical for regulating sleep-wake behavior. Their intrinsic firing activity promotes wakefulness. Orexin neurons are also specialized sensor of the body's glucose level. Small rises in glucose level inhibit intrinsic action potential firing of orexin neuron. A distinct group of orexin neuron exhibits only transient inhibitory responses to sustained glucose stimulation. This adaptation involves recovery from inhibition via closure of leak-like potassium channels. In this project, we simulated the baseline behavior and adapting/nonadapting orexin response to sustained glucose stimulation in MatLab environment.

Keywords: Orexin neurons, Mathematical, matlab.

1. Introduction

Orexin (also known as hypocretin) neurons, located in lateral hypothalamus, play a critical role in regulating sleep and wakefulness (Sakurai et al., 1998). In normal individuals, orexin neurons provide a waking drive to multiple activating systems (Eggermann et al., 2003). Their natural state is depolarized and active, by which they would promote wakefulness, and that their inhibition would be necessary for allowing sleep (Estabrooke et al., 2001). Individuals with a reduced number of orexin neurons show symptoms of narcolepsy, a chronic neurological sleep disorder characterized by excessive daytime sleepiness and a marked disorganization of sleep-wake behavior.

In addition to being able to promote wakefulness and affect other vital behaviors of the body, orexin neurons also act as electrical detectors of glucose, which is a fundamental signal of the change in body energy level (William et al., 2008). Small rises in ambient glucose level decreases the firing rate of orexin neurons (Burdakov et al., 2005). However, the double role of orexin neurons poses a paradox. As orexin neurons are key regulators of sleep-wake behavior, their loss of activity due to rises in glucose would cause narcolepsy. But on the other hand, normal wakefulness is maintained when one is experiencing rises in ambient glucose level, such as having a meal. William and colleagues (2008) proposed the presence of two types of orexin neuron, one of them being able to encode changes in stimulus levels but not unchanging (baseline) stimulus levels, a phenomenon called adaptation. This type of orexin neurons self-restores their firing after inhibition by changes in glucose level. Such adaptive glucose-sensing property of adaptive orexin neurons enables the orexin system to “filter out” baseline glucose levels while continuing to be sensitive to changes in glucose (William et al., 2008).

2. Mathematical Models and Methods

In order to investigate the intrinsic property of orexin neurons and different responses to ambient glucose changes of the two types of orexin neurons, we used a standard Hodgkin-Huxley formalism model (Williams and Diniz Behn, 2011). The equation for the change in membrane potential, dv/dt , in summed current notation, is given by

$$C \frac{dv}{dt} = I_0 - \sum_j I_j$$

where $C=1$ is the capacitance of the cell membrane, I_0 is an applied current, and I_j for $j = \{Na, K, K_2, T, h, CAN, Cal, L, GIRK\}$ are intrinsic currents. These currents have been either experimentally identified or electrophysiologically suggested (Williams and Diniz Behn, 2011).



Previous experimental work by Eggermann and colleagues (2003) has identified five intrinsic currents in orexin neurons: standard spiking sodium and potassium currents, I_{Na} and I_K , low threshold calcium current, I_T , hyperpolarization-activated current and calcium-dependent nonspecific cation current, I_h and I_{CAN} . In addition to the standard leak current I_L , we also include a calcium leak current, I_{cal} to model the possibility of calcium currents from intracellular stores of or non-voltage dependent channel. Li and colleagues (2002) suggested the presence of a slowly-inactivating potassium current, I_{K2} . Finally we include a G-protein-gated inwardly rectifying K^+ channel (GIRK) current I_{GIRK} (Li and van den Pol 2006). The formalism of each current including gating variables of activation and inactivation is provided below (William and Diniz Behn, 2011).

To simulate the mechanism of change in glucose level affecting behaviors of orexin neuron, we add a potassium leak current I_{K2P} to the single-cell model, as proposed by Burdakov and colleagues (2005) that glucose inhibition is mediated by activation of “leak” potassium channel (K_{2P}). Rises in ambient glucose can trigger large influx of potassium current through this leak-like potassium channel, causing hyperpolarization and inhibition of firing of orexin neurons. Adapting orexin cells (Type-D orexin cells) restore spontaneous firing after inhibition of glucose by closing K_{2P} channel, which does not happen in the case of nonadapting orexin cells (Type-H orexin cells).

3. Simulations and Analysis

3.1. Baseline Behavior of single-cell model

We simulated the baseline behavior of a single orexin neuron in MatLab by hardcoding governing differential equations of gating variables of each current in the system. We used the built-in ODE solver to solve and then plot the membrane potential versus time. Specifically, we set applied current $I_0 = 2$ to keep the model neuron spiking over a time period of 2000 msec (Figure 1). The model orexin neuron shows subthreshold oscillation preceding a spike, suggesting the interactions between the depolarizing I_{CAN} and the hyperpolarizing I_{K2} (William and Diniz Behn, 2011).

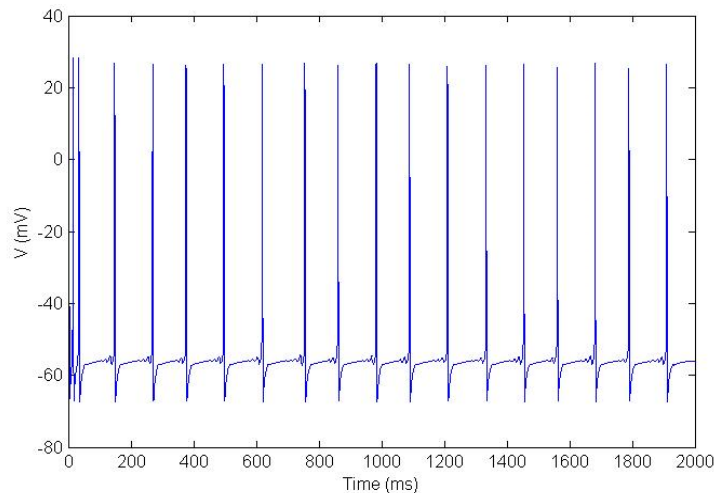


Figure 1. Model orexin neuron baseline behavior with applied current $I_0 = 2$. Subthreshold oscillation increases in amplitude until the spiking threshold is reached.

3.2. Mechanism of adaptive and nonadaptive Glucose-sensing

We first fitted the leak potassium current I_{K2P} with the Goldman-Hodgkin-Katz (GHK) current equation (Burdakov et al., 2005) in the following form :

$$I = P_K z^2 \frac{VF^2 [K^+]_j - [K^+]_o \exp(-zFV/RT)}{RT (1 - \exp(-zFV/RT))}$$

where V is membrane potential, z is the charge of potassium ion (+1), $[K^+]_j$ is the pipette K^+ concentration, $[K^+]_o$ is the ACSF K^+ concentration, T is temperature (298.15 K, corresponding to

25°C), $R = 8.314472 \text{ J/(K mol)}$ is the gas constant, and $F = 96485.3399 \text{ C/mol}$ is Faraday's constant. We set $[K^+]_j = 130$, $[K^+]_o = 2.5$, and $P_K = 0.0000176$. The experimental data for I-V plot of net glucose-activated current (Burdakov et al., 2005) and our fitted plot of I_{K2P} are shown in figure 2.

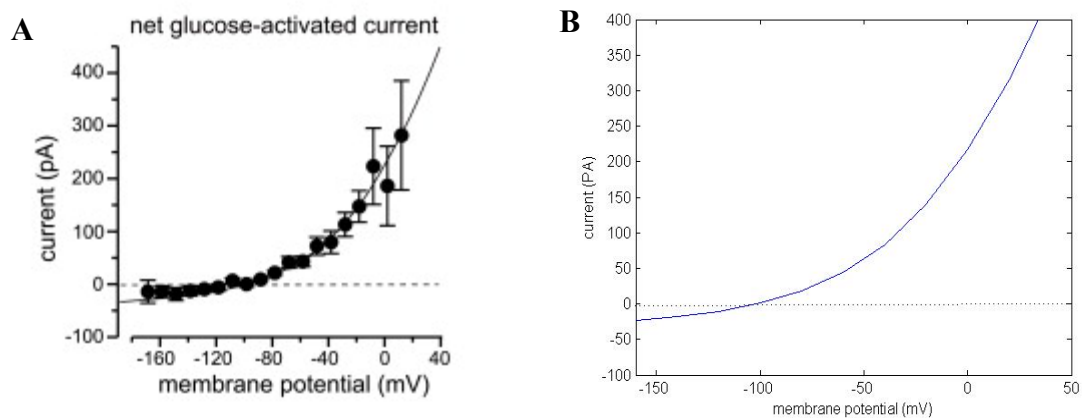


Figure 2. Fitted I-V plot of I_{K2P} compared to experimental data. A) I-V plot of net glucose-activated current B) Fit of the GHK equation to the data

We then simulated the mechanism of glucose inhibition on Type-D and Type-H orexin cells. Glucose stimulus was added to the cell at 500 msec, which was represented by keeping the leak-like potassium channel closed for 500 msec (i.e., we set $I_{K2P} = 0$) and then turning on the channel (i.e., we reset I_{K2P} to fitted equation) for both cells. To simulate the sustained inhibition on Type-H orexin cell, we kept the K_{2P} channel open for the rest of the time (i.e., $I_{K2P} = 0$ for $t > 500$ and $t < 2000$). The response of modeled Type-H cell is shown in figure 3B. From the plot, the model Type-H orexin cell was completely inhibited by glucose stimulus.

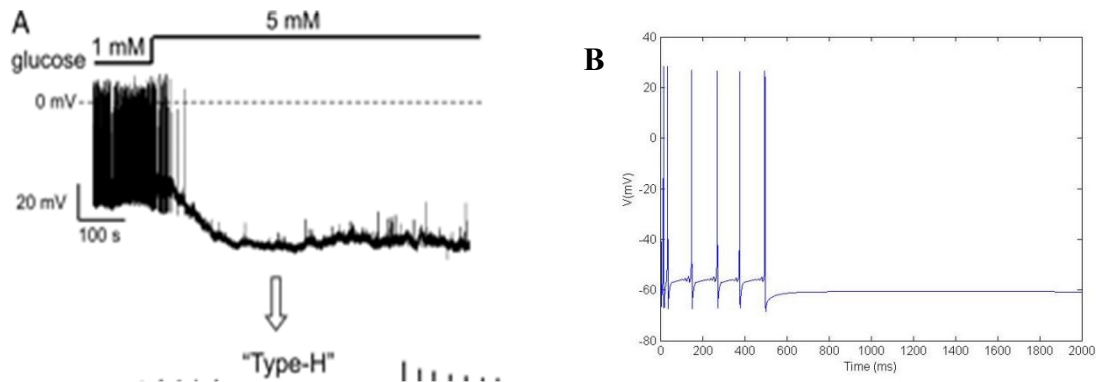


Figure 3. Type-H (nonadapting) orexin cells. A) Nonadaptive membrane potential response to glucose(Williams et al., 2008). B) Model Type-H orexin cell inhibited by leak-like potassium current I_{K2P} .

We simulated the adaptation of Type-D orexin cells by closing the leak-like potassium channel 500 msec after glucose stimulation (i.e., we set $I_{K2P} = 0$ again at $t = 1000$). The response of modeled Type-D cell is shown in figure 4B. Upon closure of I_{K2P} channel, Type-D orexin cell was able to restore its intrinsic spontaneous firing as in experiment.

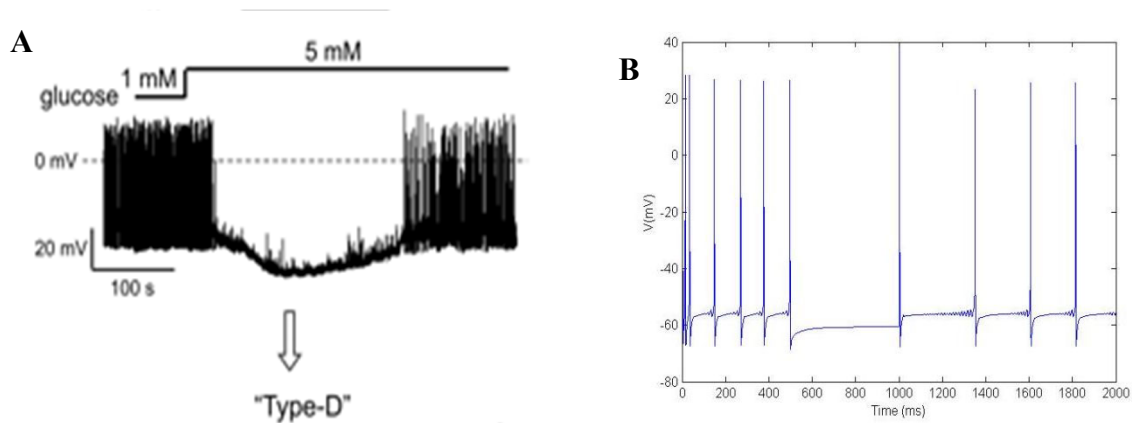


Figure 4. Type-D (adapting) orexin cells. A) Adaptive membrane potential response to glucose(Williams et al., 2008). B) Model Type-D orexin cell inhibited by leak-like potassium current I_{K2P} from $t=500$ to $t=1000$, and then restores intrinsic spontaneous firing.

4. Discussion and Future Work

We have simulated the baseline behavior of a single-cell orexin using a standard Hodgkin-Huxley formalism and simulated the mechanism of adaptive glucose-sensing by adding a leak-like potassium current to the model. Response of both model Type-D orexin cell and Type-H orexin cell to glucose stimulation corresponds to experimental data. However, there is discrepancy between the baseline behavior of model orexin neuron and experimental results. Model orexin neuron requires an applied current to maintain its firing, whereas experimental work by Eggermann and colleagues (2003) showed that orexin neuron intrinsically fires at 1 to 2 Hz in the absence of applied current. Additional work to modify MatLab code for the model will provide more accurate simulations of both orexin neuron intrinsic properties and adaptive glucose-sensing mechanism.

References

- [1] Burdakov D, et al. (2006) Tandem-pore K^+ channels mediate inhibition of orexin neurons by glucose. *Neuron* 50:711-722.
- [2] Eggermann, E; Bayer, L; Serafin, M; Sain-Mleux, B; Bernheim, L; Machard, D; Jones, B. E; Muhlethaler, M. (2003) The Wake-Promoting Hypocretin-Orexin Neurons Are in an Intrinsic State of Membrane Depolarization. *J. of Neuroscience* 23: 1557-1562.
- [3] Li Y, Gao XB, Sakurai T, and van den Pol AN (2002) Hypocretin/orexin excites hypocretin neurons via a local glutamate neuron-A potential mechanism for orchestrating the hypothalamic arousal system. *Neuron* 36:1169-1181.
- [4] Li Y and van den Pol AN (2006) Differential target-dependent actions of coexpressed inhibitory dynorphin and excitatory hypocretin/orexin neuropeptides. *J Neuroscience* 26:13037-13047.
- [5] Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, Williams SC, Richardson JA, Kozlowski GP, Wilson S, et al (1998) Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein coupled receptors that regulate feeding behavior. *Cell* 92:573-585.
- [6] Williams RH, Alexopoulos H, Jensen LT, Fugger L, and Burdakov D (2008) Adaptive sugar sensors in hypothalamic feeding circuits. *Proceedings of National Academy of Sciences U.S.A* 105: 11975-11980.
- [7] Williams KS, Behn CG (2011) Dynamic interactions between orexin and dynorphin may delay onset of functional orexin effects: a modeling study. *J Biol Rhythms* 26:171-181.