Supplemental Material

Modeling of slow activated Ca^{2+}-sensitive K^+ channels dependent bursting and $[Ca^{2+}]_c$ oscillations

Equations and coefficients for channels and pumps are taken from previous model (1) or represented in this supplemental material. Slow activated Ca^{2+}-sensitive K^+ channels were modeled as well as the fast activated Ca^{2+}-sensitive K^+ channels with considerably increased time-dependent parameters for activation reported in (2).

The units are: time in milliseconds (ms), voltage in millivolts (mV), concentration in micromoles/liter (μM), current in femtoamperes (fA), conductance in picosiemens (pS), capacitance in femtofarads (fF). Numerical integration of the model was carried out using standard numerical methods (1). This model is available for direct simulation on the website "Virtual Cell" (www.nrcam.uchc.edu) in available for direct simulation on the website "Virtual Cell" (www.nrcam.uchc.edu) in "MathModel Database" on the "math workspace" in the library "Fridlyand" with name "SlowCa2+acted Kchan".

***Ca^{2+} current* (I_{VCa}).**

$$I_{VCa} = g_{mVCa}\, d_{Ca}\, f_{VCa}\, (V_P - E_{Ca}) \quad (1)$$

$$\frac{d\, d_{Ca}}{dt} = \frac{d_{Cab} - d_{Ca}}{\tau_{dCa}} \quad (2)$$

$$d_{Cab} = \frac{1}{1 + \exp[(2 - V_P)/10.5]} \quad (3)$$

$$\tau_{dCa} = 2.2\text{-}1.79{*}\exp\text{-}[(V_P - 9.7)/70.2]^2 \quad (4)$$

$$f_{VCa} = f_{VCab} = \frac{1}{1 + \exp[(-15 + V_P)/6]} \quad (5)$$

where g_{mVCa} = 800 pS, E_{Ca} = 100 mV.

Delayed Rectifier K^+ current (I_{Kr}).

$$I_{Kr} = g_{mKr}\, d_{Kr}^2\, f_{Kr}\, (V_P - E_K), \quad (6)$$

$$\frac{d\, d_{Kr}}{dt} = \frac{d_{Krb} - d_{Kr}}{\tau_{dKr}} \quad (7)$$

$$d_{Krb\infty} = \frac{1}{1 + \exp[(-9 - V_P)/5]} \quad (8)$$

where g_{mKr} = 30000 pS, τ_{dKr} = 23 mc, E_K = -75 mV.

Fast Ca^{2+}-activated K^+ current *(I_{KCa})*

$$I_{KCa} = g_{mKCa}\, d_{KCa}\, (V_P - E_K), \quad (9)$$

$$d_{KCa} = \frac{[[Ca^{2+}]_c^4}{[Ca^{2+}]_c^4 + (0.25)^4} \quad (10)$$

where g_{mKCa} = 10 pS.

Slow activated Ca^{2+}-sensitive K^+ channels

$$I_{KCas} = g_{mKCas}\, d_{KCas}\, (V_P - E_K), \quad (11)$$

$$\frac{d\, d_{KCas}}{dt} = \frac{d_{KCasb} - d_{KCas}}{\tau_{dKCas}} \quad (12)$$

$$d_{KCab} = \frac{[Ca^{2+}]_c^4}{[Ca^{2+}]_c^4 + (0.25)^4} \quad (13)$$

where g_{mKCas} = 90 pS, τ_{dKCas} =2300 mc.

ATP-sensitive K^+ channels current (I_{KATP}).

$$I_{KATP} = g_{mKATP}\, O_{KATP}\, (V_P - E_K), \tag{14}$$

where.

$$O_{KATP} = \frac{0.08\,(1 + 2\,[MgADP_f]_i/17) + 0.89\,([MgADP_f]_i/17)^2}{(1 + [MgADP_f]_i/17)^2(1 + 0.45\,[MgADP_f]_i/26 + [ATP_{free}]_i/50)} \tag{15}$$

$$[MgADP_f]_i = 0.55\,[ADP_f]_i \tag{16}$$

where O_{KATP} is the fraction of open K_{ATP} channels, $[MgADP_f]_i$ is the concentrations of free Mg-bound ADP , g_{mKATP} =30000 pS, $[ADP_f]_i$ = 20 μM.

Plasma membrane Ca^{2+} pump current (I_{Cap}).

$$I_{Cap} = P_{mCap} \frac{[Ca^{2+}]_{ci}^2}{[Ca^{2+}]_c^2 + (0.2)^2} \tag{17}$$

where P_{mCap} = 4300 fA

Na^+ background current *(I_{Nab})*

$$I_{Nab} = g_{mNab}\,(V_P - E_{Na}) \tag{18}$$

where g_{mNab} = 12 pS, E_{Na} = -70 mV.

The differential equation describing time-dependent changes in the plasma membrane potential (V_p) is the current balance equation:

$$-C_m \frac{dV_p}{dt} = I_{VCa} + I_{Kr} + I_{KATP} + I_{KCa} + I_{KCas} + I_{Cap} + I_{Nab} \tag{19}$$

where C_m is the whole cell membrane capacitance. The PM currents are listed in Figure1.

Based on the consideration in our general model (41) and including only I_{VCa} and I_{Cap}, the equations for $[Ca^{2+}]_i$ dynamics can be written as:

$$\frac{d[Ca^{2+}]_c}{dt} = \frac{f_i\,(-I_{VCa} - 2\,I_{Cap})}{2\,F\,V_i} - k_{sg}\,[Ca^{2+}]_c \tag{20}$$

where f_i is the fraction of free Ca^{2+} in cytoplasm, F is Faraday's constant, V_i is the effective volumes of the cytosolic compartment, and k_{sg} is a coefficient of the sequestration rate of $[Ca^{2+}]_c$.

REFERENCES

1. Fridlyand LE, Tamarina N, and Philipson LH. Modeling of Ca2+ flux in pancreatic beta-cells: role of the plasma membrane and intracellular stores. *Am J Physiol Endocrinol Metab* 285: E138-154, 2003.

2. Gopel SO, Kanno T, Barg S, Eliasson L, Galvanovskis J, Renstrom E, and Rorsman P. Activation of Ca(2+)-dependent K(+) channels contributes to rhythmic firing of action potentials in mouse pancreatic beta cells. *J Gen Physiol* 114: 759-770, 1999.