Supplementary Materials for

A computational model predicts sex-specific responses to calcium channel blockers in mesenteric vascular smooth muscle

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This PDF file includes all equations and parameters of the Hernandez-Hernandez model.

S1. Male voltage-gated calcium current ($\mathbf{I_{Cav2.1}}$) model equations.

Parameters	Values
Initial conditions (dL, dF)	(0.0062, 07450)
Activation parameters (x_1, x_2, x_3, x_4, x_5)	(0.3321, 12.9372, 0.1557, -10.3606, 1.763)
Inactivation parameters (x_1, x_2, x_3, x_4, x_5)	(0.0028, -54.1923, 0.0111, 22.3706, 74.28)

Table 1. Male parameters of $\mathrm{I_{Cav2.1}}$

Male activation gate equations

$$alpha_{act} = 0.3321 * e^{\left(\frac{V}{12.9372}\right)};$$

$$beta_{act} = 0.1557 * e^{\left(\frac{V}{-10.3606}\right)};$$

$$dL_{bar} = \frac{1}{1 + \left(\frac{beta_{act}}{alpha_{act}}\right)};$$

$$tau_{dL} = \frac{1}{alpha_{act} + beta_{act}} + 1.763;$$

Male inactivation gate equations

$$alpha_{ina} = 0.0028 * e^{\frac{V}{-54.1923}};$$

$$beta_{ina} = 0.0111 * e^{\frac{V}{22.3706}};$$

$$dF_{bar} = \frac{1}{1+\left(\frac{beta_{ina}}{alpha_{ina}}\right)};$$

$$tau_{dF} = \frac{1}{alpha_{ina}+ beta_{ina}} + 74.28;$$

Activation and inactivation differential equations

$$\frac{dL}{dt} = \left(\frac{dL_{bar}- dL}{tau_{dL}}\right);$$

$$\frac{dF}{dt} = \left(\frac{dF_{bar}- dF}{tau_{dF}}\right);$$

The male voltage-gated calcium current is given by

$$I_{CaV,M} = 0.22 * dL * dF * \left(\frac{F^2}{R*T}\right) * Vm * \left(\frac{\left(Ca_i * e^{\left(\frac{z_{Ca}*F*Vm}{R*T}\right)} - Ca_{out}\right)}{e^{\left(\frac{z_{Ca}*F*Vm}{R*T}\right)} - 1.}\right) \quad \text{(Eq. 3.9)}$$

S2. Female voltage-gated calcium male current ($\mathrm{I_{Cav2.1}}$) model equations.

Parameters	**Values**
Initial conditions (dL, dF)	(0.0062, 07450)
Activation parameters (x_1, x_2, x_3, x_4, x_5)	(0.4278, 10.8837, 0.1938, -11.5189, 1.8555)
Inactivation parameters (x_1, x_2, x_3, x_4, x_5)	(0.0032, -44.637, 0.0117, 30.4336, 68.7682)

Table 2. Female parameters of $\mathrm{I_{Cav2.1}}$

Female activation gate equations

$$alpha_{act} = 0.4278 * e^{\left(\frac{V}{10.8837}\right)};$$

$$beta_{act} = 0.1938 * e^{\left(\frac{V}{-11.5189}\right)};$$

$$dL_{bar} = \frac{1}{1 + \left(\frac{beta_{act}}{alpha_{act}}\right)};$$

$$tau_{dL} = \frac{1}{alpha_{act} + beta_{act}} + 1.8555;$$

Female inactivation gate equations

$$alpha_{ina} = 0.0028 * e^{\frac{V}{-54.1923}};$$

$$beta_{ina} = 0.0111 * e^{\frac{V}{22.3706}};$$

$$dF_{bar} = \frac{1}{1+\left(\frac{beta_{ina}}{alpha_{ina}}\right)};$$

$$tau_{dF} = \frac{1}{alpha_{ina} + beta_{ina}} + 74.28;$$

Activation and inactivation differential equations

$$\frac{dL}{dt} = \left(\frac{dL_{bar} - dL}{tau_{dL}}\right);$$

$$\frac{dF}{dt} = \left(\frac{dF_{bar} - dF}{tau_{dF}}\right);$$

The female voltage-gated calcium male current is given by

$$I_{CaV,F} = 0.38 * dL * dF * \left(\frac{F^2}{R*T}\right) * V * \left(\frac{\left(Ca_i * e^{\left(\frac{z_{Ca}*F*Vm}{R*T}\right)} - Ca_{out}\right)}{e^{\left(\frac{z_{Ca}*F*Vm}{R*T}\right)} - 1.}\right) \quad \text{(Eq. 3.10)}$$

S3. Male voltage-gated potassium current ($I_{Kv2.1}$) model equations.

Parameters	**Values**
Initial conditions (p_{K21})	(0.0001)
Activation parameters (x_1, x_2, x_3, x_4, x_5)	(0.0404 10.5223 0.0355 221.4551 11.4616)
G_{K21}	0.7 (nS)

Table 3. Male parameters of $I_{Kv2.1}$

Male activation gate equations

$$alpha_x = 0.0404 * e^{\left(\frac{V}{10.5223}\right)}$$

$$beta_x = 0.0355 * e^{\left(\frac{V}{221.4151}\right)}$$

$$p_{Kbar} = \frac{1}{1+\left(\frac{beta_x}{alpha_x}\right)}$$

$$tau_{p_K} = \frac{1}{alpha_x + beta_x} + 11.4616$$

$$\frac{dp_{K21}}{dt} = \left(\frac{p_{Kbar} - p_K}{tau_{p_K}}\right)$$

The male voltage-gated $K_{v2.1}$ potassium current is given by

$$I_{Kv21,M} = G_{K21} * p_{K21} * (V - E_K) \quad \text{(Eq. 3.11)}$$

S4. Female voltage-gated potassium current ($I_{Kv2.1}$) model equations.

Parameters	**Values**
Initial conditions (p_{K21})	(0.0001)
Activation parameters (x_1, x_2, x_3, x_4, x_5)	(0.0717 12.9290 0.0533 191.7326 0.3489)
G_{K21}	1.8 (nS)

Table 4. Female parameters of $I_{Kv2.1}$

Female activation gate equations

$$alpha_x = 0.0717 * e^{\left(\frac{V}{12.9290}\right)}$$

$$beta_x = 0.0533 * e^{\left(\frac{V}{191.7326}\right)}$$

$$p_{Kbar} = \frac{1}{1+\left(\frac{beta_x}{alpha_x}\right)}$$

$$tau_{p_K} = \frac{1}{alpha_x + beta_x} + 0.3489$$

$$\frac{dp_{K21}}{dt} = \left(\frac{p_{Kbar} - p_K}{tau_{p_K}}\right)$$

The female voltage-gated $K_{v2.1}$ potassium current is given by

$$I_{Kv21,F} = G_{K21} * p_{K21} * (V - E_K) \qquad \text{(Eq. 3.12)}$$

S5. Male voltage-gated potassium current ($I_{Kv1.5}$) model equations.

Parameters	**Values**
Initial conditions (p_{K15})	(0.0001)
Activation parameters (x_1, x_2, x_3, x_4, x_5)	(0.0717 12.9290 0.0533 191.7326 0.3489)
G_{K15}	1.8 (nS)

Table 5. Male parameters of $I_{Kv1.5}$

Male activation gate equations

$$alpha_x = 0.0717 * e^{\left(\frac{V}{12.9290}\right)}$$

$$beta_x = 0.0533 * e^{\left(\frac{V}{191.7326}\right)}$$

$$p_{Kbar} = \frac{1}{1+\left(\frac{beta_x}{alpha_x}\right)}$$

$$tau_{p_K} = \frac{1}{alpha_x+beta_x} + 0.3489$$

$$\frac{dp_{K15}}{dt} = \left(\frac{p_{Kbar}-p_K}{tau_{p_K}}\right)$$

The male voltage-gated $K_{v2.1}$ potassium current is given by

$$I_{Kv15,M} = G_{K15} * p_{K15} * (V - E_K) \qquad \text{(Eq. 3.13)}$$

S6. Female voltage-gated potassium current ($I_{Kv1.5}$) model equations.

Parameters	Values
Initial conditions (p_{K15})	(0.0001)
Activation parameters (x_1, x_2, x_3, x_4, x_5)	(0.0666 9.6398 0.0637 123.4370 -0.0015)
G_{K15}	1.5 (nS)

Table 6. Female parameters of $I_{Kv1.5}$

Female activation gate equations

$$alpha_x = 0.0666 * e^{\left(\frac{V}{9.6398}\right)}$$

$$beta_x = 0.0637 * e^{\left(\frac{V}{123.4370}\right)}$$

$$p_{Kbar} = \frac{1}{1+\left(\frac{beta_x}{alpha_x}\right)}$$

$$tau_{p_K} = \frac{1}{alpha_x+beta_x} - 0.0015$$

$$\frac{dp_{K15}}{dt} = \left(\frac{p_{Kbar} - p_K}{tau_{p_K}}\right)$$

The female voltage-gated $K_{v2.1}$ potassium current is given by

$$I_{Kv15,F} = G_{K15} * p_{K15} * (V - E_K) \qquad \text{(Eq. 3.14)}$$

S7. The large-conductance Ca-sensitive potassium (BK_{Ca}) current model equations.

Parameter	Value	Description
BK_T	8(male) & 6(female)	Number of BK_{Ca} channels
$perm_{BKCa}$	4.00E-13	Permeability of BK_{Ca} channels (cm^3/s)

Table 7. Parameters of I_{BKCa}

$$xabss_z = \left(-\frac{0.681249}{1.0+\left(\frac{Ca_{jun}*1000.0-0.218988}{0.428335}\right)*\left(\frac{Ca_{jun}*1000.0-0.218988}{0.428335}\right)} + \frac{1.40001}{1.0+\left(\frac{Ca_{jun}*1000.0+228.71}{684.946}\right)*\left(\frac{Ca_{jun}*1000.0+228.71}{684.946}\right)}\right)$$

$$xabss_{vh} = \left(\frac{8540.23}{\left(\left(\frac{Ca_{jun}*1000.0+0.401189}{0.00399115}\right)^{0.668054}\right)}\right) - 109.28;$$

$$xabss = \left(\frac{1.0}{1.0+e^{\wedge}\left(-xabss_z*\frac{F*V-xabss_{vh}}{R*T}\right)}\right)$$

$$xabtc = \left(\frac{13.8049}{1.0 + \left(\frac{V - 153.019}{66.4952}\right) * \left(\frac{V - 153.019}{66.4952}\right)} \right)$$

$$\frac{dx_{ab}}{dt} = \left(\frac{xabss - x_{ab}}{xabtc} \right)$$

The large-conductance Ca^{2+}-sensitive potassium current (I_{BKCa}) is given by

$$I_{BKCa} = BK_T * Perm_{BKCa} * x_{ab} * \left(\frac{z_K^2 F^2}{R*T}\right) * V * \left(\frac{\left(K_{in} * e^{\left(\frac{z_{Ca}*F*Vm}{R*T}\right)} - K_{out} \right)}{e^{\left(\frac{z_{Ca}*F*Vm}{R*T}\right)} - 1.} \right) \text{(Eq. 3.15)}$$

S8. The nonselective cations currents (I_{NSC}) model equations.

Parameter	Value	Description
PnsK	1.3	Permeability of K^+
PnsNa	0.9	Permeability of Na^+
gnsNa	0.5	Conductance ratio of Na^+
gnsK	0.1	Conductance ratio of K^+
gns	4.92 (varies)	Maximum Conductance (nS)

Table 8. Parameters of I_{NSC}

The reversal potential (E_{NSC}) of the I_{NSC} is described by

$$E_{NSC} = \left(R * \frac{T}{F}\right) * log\left(\frac{PnsK*K_{out} + PnsNa*Na_{out}}{PnsK*K_{in} + PnsNa*Na_{in}}\right)$$

The total nonselective cations current (I_{NSC}) is given by

$$I_{NSC} = (gnsNa) * gns * \left(V - (E_{nscc})\right) + (gnsK) * gns * (V - (E_{nscc})) \qquad \text{(Eq. 3.16)}$$

S9. Leak currents model equations.

Parameter	Value	Description
$G_{K,b}$	0.009	Maximum Conductance of K^+ (nS)
$G_{Na,b}$	0.001	Maximum Conductance of Na^+ (nS)
$G_{Ca,b}$	0.00256	Maximum Conductance of Ca^{2+} (nS)

Table 9. Parameters of leak currents

$$I_{Ca,b} = G_{Ca,b} * (V - E_{Ca}) \qquad \text{(Eq. 3.17)}$$

$$I_{Na,b} = G_{Na,b} * (V - E_{Na}) \qquad \text{(Eq. 3.18)}$$

$$I_{K,b} = G_{K,b} * (V - E_K) \qquad \text{(Eq. 3.19)}$$

S10. Pumps and transporters model equations.

The sodium-potassium pump (I_{NaK}) current model equations.

Parameter	Value	Description
$I_{NaK_{max}}$	104.16	Maximum NaK current (pA)
$KmNaK_K$	1.6	Potassium selectivity (mM)
$KmNaK_{Na}$	22	Sodium selectivity (mM)
Q10	1.87	Q10 coefficient

Table 10. Parameters of I_{NaK}

$$N_{pow} = \left(Q10^{\frac{T-309.2}{10}}\right);$$

$$N_1 = \frac{(K_{out}^{1.1})}{K_{out}^{1.1} + KmNaK_K^{1.1}};$$

$$N_2 = \frac{(Na_{in}^{1.7})}{Na_{in}^{1.7} + KmNaK_{Na}^{1.7}};$$

$$N_0 = \frac{1.0}{1 + \left(0.1245 * exp\left(-0.1 * V * \frac{F}{R * T}\right)\right) + \left(2.19e - 3 * \left(e^{\left(\frac{Na_{out}}{49.71}\right)}\right) * e^{\left(-1.9 * V * \frac{F}{R * T}\right)}\right)};$$

$$I_{NaK} = I_{NaK_{max}} * N_1 * N_2 * N_0 * N_{pow} \qquad \text{(Eq. 3.16)}$$

The sodium-calcium exchanger (I_{NCX}) current model equations.

Parameter	Value	Description
P_{NCX}	0.0003	Maximum NCX current (pA)
gammax	1.6	coefficient

Table 11. Parameters of I_{NCX}

$$phi_F = exp\left(gammax * V * \frac{F}{R*T}\right)$$

$$phi_R = exp\left((gammax - 1) * V * \frac{F}{R*T}\right)$$

$$X_{NCX} = \frac{(Na_{in}^3)*Ca_{out}*phi_F - (Na_{out}^3)*Ca_i*phi_R}{1+0.0003*\left((Na_{out}^3)Ca_{in}+(Na_{in}^3)*Ca_{out}\right)};$$

$$I_{NCX} = P_{NCX} * X_{NCX} \qquad \text{(Eq. 3.17)}$$

The sarcolemma calcium pump (I_{PMCA}) current.

Parameter	Value	Description
$I_{PMCAbar}$	2.8	Maximum PMCA current (pA)
K_{mPMCA}	170E-6	Calcium binding capacity (mM)

Table 12. Parameters of I_{PMCA}

$$I_{PMCA} = I_{PMCAbar} * \frac{Ca_i^2}{Ca_i^2+K_{mPMCA}^2} \qquad \text{(Eq. 3.18)}$$

The flux of model J_{SERCA} equations.

Parameter	Value	Description
$I_{SERCAbar}$	5.25E-6	Maximum SERCA flux
K_{mSERCA}	219E-6	Calcium binding capacity (mM)

Table 13. Parameters of J_{SERCA}

$$J_{SERCA_{ALL}} = I_{SERCAbar} * \left(\frac{Ca_i^2}{Ca_i^2+K_{mSERCA}^2}\right) \qquad \text{(Eq. 3.19)}$$

S12. Ryanodine receptor flux (J_{RyR}) model equations.

Parameter	Value	Description
n_RyR_Ca_jun	1.2	
Ca_{TH}	0.12	SR Load Ca threshold (mM)
Kd	500	Calcium binding capacity (1/mM*ms)
V_{RyR}	0.0022	Maximum RyR release rate (1/ms)
$V_{jun-cyt}$	0.0008	Maximum Ca diffusion rate from junctional region to cytosol (1/ms)

Table 14. Parameters of J_{RyR}

$$\mathrm{Y_{SR}} = \frac{1}{1 + \left(\frac{Ca_{TH}}{[Ca]_{SR}}\right)^{5}}$$

$$\tau_n = \frac{1}{\alpha + \beta} = \frac{1}{K_d\left(Ca_{jun}^{\mathrm{n\_RyR\_Ca\_jun}}\ \mathrm{Y_{SR}} + \mathrm{Ca}_{\mathrm{jun_{TH}}}^{\mathrm{n\_RyR\_Ca\_jun}}\right)}$$

$$n_\infty = \frac{\alpha}{\alpha + \beta} = \frac{K_d Ca_{jun}^{\mathrm{n\_RyR\_Ca\_jun}}}{K_d\left(Ca_{jun}^{\mathrm{n\_RyR\_Ca\_jun}}\ \mathrm{Y_{SR}} + \mathrm{Ca}_{\mathrm{jun_{TH}}}^{\mathrm{n\_RyR\_Ca\_jun}}\right)} = \frac{Ca_{jun}^{\mathrm{n\_RyR\_Ca\_jun}}\ \mathrm{Y_{SR}}}{\left(Ca_{jun}^{\mathrm{n\_RyR\_Ca\_jun}}\ \mathrm{Y_{SR}} + \mathrm{Ca}_{\mathrm{jun_{TH}}}^{\mathrm{n\_RyR\_Ca\_jun}}\right)}$$

$$\frac{dn}{dt} = \frac{n_\infty - n}{\tau_n}$$

$$J_{RyR} = V_{RyR} * n * (Ca_{SR} - Ca_{jun}) \qquad \text{(Eq. 3.20)}$$

$$J_{jun-cyt} = V_{jun-cyt} * (Ca_{jun} - Ca_i) \qquad \text{(Eq. 3.21)}$$