Ca^{2+} Effects on ATP Production and Consumption Have Key Regulatory Roles on Oscillatory Islet Activity

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SUPPORTING MATERIAL

1 Derivation of the Glycolytic Model

Glycolysis plus efflux of pyruvate through mitochondrial pyruvate dehydrogenase complex may be depicted, assuming the reaction catalyzed by triose phosphate isomerase is at equilibrium and that the concentrations of its product and substrate are equal, with the reaction scheme in Fig. 1 with labels given in Table 1.

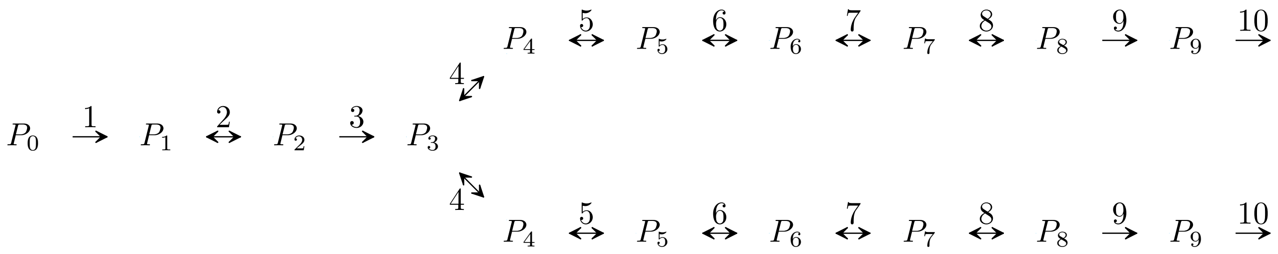

Figure 1: Reaction scheme for glycolysis plus efflux of pyruvate through mitochondrial pyruvate dehydrogenase complex.

Then, a system of differential equations for the reaction scheme, where P_i is the total concentration of product i and J_i is the total flux (concentration per time) through enzyme i, is

$$[P_i]' = J_i - J_{i+1} \qquad \text{for } 1 \le i \le 9, i \ne 3$$
$$[P_3]' = J_3 - \frac{1}{2}J_4.$$

Assuming the reaction catalyzed by enzyme 2 (glucose 6-phosphate isomerase) is at equilibrium so that $[P_1] = k_{12}[P_2]$ and $[P_1]' = k_{12}[P_2]'$,

$$[P_1]' + [P_2]' = J_1 - J_3$$
$$[P_2]'(k_{12} + 1) = J_1 - J_3$$
$$[P_2]' = \frac{1}{k_{\text{GPI}} + 1}(J_1 - J_3)$$

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i	Enzyme i	Product P_i
0	—	glucose
1	glucokinase (GK)	glucose 6-phosphate
2	glucose 6-phosphate isomerase (GPI)	fructose 6-phosphate (F6P)
3	phoshphofructokinase (PFK)	fructose 1,6-bisphosphate (FBP)
4	aldolase	glyceraldehyde 3-phosphate
4^*	triose phosphate isomerase	dihydroxyacetone phosphate
5	glyceraldehyde 3-phosphate dehydrogenase	1,3-bisphosphoglycerate
6	phosphoglycerate kinase	3-phosphoglycerate
7	phosphoglycerate mutase	2-phosphoglycerate
8	enolase	phosphoenolpyruvate
9	pyruvate kinase	pyruvate (PYR)
10	pyruvate dehydrogenase (PDH)	—

Table 1: Enzymes and products of glycolysis plus pyruvate dehydrogenase. Each glycolytic enzyme has been labeled with its product except that enzyme 4 (aldolase) has two products: P_4 (glyceraldehyde 3-phosphate) and P_{4^*} (dihydroxyacetone phosphate), and that P_4 (glyceraldehyde 3-phosphate) is the product of two enzymes: enzyme 4 (aldolase) and enzyme 4^* (triose phosphate isomerase). Reaction 4^* is not shown in the reaction scheme of Fig. 8.

where $k_{\text{GPI}} = k_{12}$. Assuming the reactions catalyzed by enzymes 4 through 9 downstream to PFK are at equilibrium so that $[P_i] = k_{ij}[P_j]$ and $[P_i]' = k_{ij}[P_j]'$ for $3 \leq i, j \leq 9$,

$$[P_3]' + \frac{1}{2}\left([P_4]' + \cdots + [P_9]'\right) = J_3 - \frac{1}{2}J_{10}$$

$$[P_3]'\left(1 + \frac{1}{2}(k_{43} + \cdots + k_{93})\right) = J_3 - \frac{1}{2}J_{10}$$

$$[P_3]' = \frac{1}{1 + \sum k_P}\left(J_3 - \frac{1}{2}J_{10}\right)$$

where $\sum k_P = \frac{1}{2}(k_{43} + \cdots + k_{93})$. That is,

$$[\text{F6P}]' = \frac{1}{1 + k_{\text{GPI}}}(J_{\text{GK}} - J_{\text{PFK}})$$

$$[\text{FBP}]' = \frac{1}{1 + \sum k_P}(J_{\text{PFK}} - \frac{1}{2}J_{\text{PDH}}).$$

2 Model Equations and Parameters

Glycolysis:

$$
\begin{aligned}
d[\text{F6P}]/dt &= (1 + k_{\text{GPI}})^{-1}(J_{\text{GK}} - J_{\text{PFK}}) \\
d[\text{FBP}]/dt &= (1 + k_{\text{LG}})^{-1}(J_{\text{PFK}} - J_{\text{PDH}}/2) \\
J_{\text{PFK}} &= V_{\text{PFK}}((1 - k_{\text{PFK}})w_{1110} + k_{\text{PFK}} \textstyle\sum_{i,j,l\in\{0,1\}} w_{ij1l})/\textstyle\sum_{i,j,k,l\in\{0,1\}} w_{ijkl} \\
w_{ijkl} &= \frac{([\text{AMP}]/K_{\text{PFK}}^{\text{AMP}})^i([\text{FBP}]/K_{\text{PFK}}^{\text{FBP}})^j([\text{F6P}]^2/K_{\text{PFK}}^{\text{F6P}})^k([\text{ATP}_c]^2/K_{\text{PFK}}^{\text{ATP}})^l}{f_{\text{AMP}}^{ik} f_{\text{FBP}}^{jk} f_{\text{MT}}^{il} f_{\text{BT}}^{jl} f_{\text{ATP}}^{kl}} \\
J_{\text{PDH}} &= k_{\text{PDH}}[\text{PYR}]^{1/2}(1 + k_{\text{PDH}}^{Ca}/[Ca_m])^{-1}
\end{aligned}
$$

ATP Production/Hydrolysis:

$$
\begin{aligned}
d[\text{ATP}_c]/dt &= J_{\text{ANT}} - J_{hyd} \\
J_{\text{ANT}} &= Vol_{m:cyt}V_{\text{ANT}}(1 + k_{\text{ANT}}^{A_m}[\text{ADP}_m]/[\text{ATP}_m])^{-1}\exp(\psi_m F/(2RT)) \\
J_{hyd} &= (k_{hyd,bas} + k_{hyd}^{Ca}[Ca_c])[\text{ATP}_c] \\
[\text{ADP}_m] &= q_1[Ca_c] + q_2\exp(-J_{\text{PDH}}/q_3) \\
A_{m,tot} &= [\text{ADP}_m] + [\text{ATP}_m]
\end{aligned}
$$

Ionic Currents:

$$
\begin{aligned}
dV/dt &= (I_{Ca(V)} + I_{K(V)} + I_{K(Ca)} + I_{K(\text{ATP})})/C_m \\
dn_{K(V)}/dt &= (n_{K(V),\infty} - n_{K(V)})/\tau_{K(V)} \\
d[Ca_c]/dt &= k_{cyt}^{Ca}(J_{\text{PM}} - J_{\text{ER}}) \\
d[Ca_{\text{ER}}]/dt &= k_{\text{ER}}^{Ca}Vol_{cyt:\text{ER}}J_{\text{ER}} \\
I_{i(s)} &= g_{i(s)}n_{i(s)}\cdot(V - V_i), \quad i(s)\in\{Ca(V),K(V),K(Ca),K(\text{ATP})\} \\
n_{i(s),\infty} &= (1 + (k_{i(s)}/r(s))^{h_{i(s)}})^{-1}, \quad i(s)\in\{Ca(V),K(V),K(Ca)\} \\
n_{i(s)} &= n_{i(s),\infty} \text{ for } i(s)\in\{Ca(V),K(V)\} \\
r(s) &= \begin{cases} e^s & \text{if } s = V \\ [s] & \text{otherwise} \end{cases} \\
n_{K(\text{ATP})} &= 20\frac{0.08(1 + 2[\text{MgADP}^-]/kdd) + 0.89([\text{MgADP}^-]/kdd)^2}{(1 + [\text{MgADP}^-]/kdd)^2(1 + [\text{ADP}^{3-}]/ktd + [\text{ATP}^{4-}]/ktt)} \\
[\text{MgADP}^-] &= 0.0164[\text{ADP}_c], \quad [\text{ADP}^{3-}] = 0.135[\text{ADP}_c], \quad [\text{ADP}^{4-}] = 0.05[\text{ATP}_c] \\
J_{\text{PM}} &= -(I_{Ca(V)}/(2F) - k_{\text{PMCA}}[Ca_c]) \\
J_{\text{ER}} &= k_{\text{ER},in}[Ca_c] - k_{\text{ER},out}([Ca_{\text{ER}}] - [Ca_c]) \\
[Ca_m] &= k_{Ca}[Ca_c]
\end{aligned}
$$

Parameter	Value	Parameter	Value	Parameter	Value
J_{GK}	9.45×10^{-2} μM/s	$\sum k_P$	0.5	$h_{Ca(V)}$	0.08
V_{PFK}	0.9 μM/s	$A_{c,tot}$	2.5 mM	$g_{K(V)}$	486 pS
V_{PDH}	0.37 μM/s	$A_{m,tot}$	15 mM	$v_{K(V)}$	-16 mV
k_{GPI}	6.33	AMP	0.5 mM	$h_{K(V)}$	0.2
k_{PFK}	0.06	V_{ANT}	72.45 μM/s	$\tau_{K(V)}$	111 ms
$k_{\text{PFK}}^{\text{AMP}}$	30 μM	$k_{\text{ANT}}^{A_m}$	2	$g_{K(Ca)}$	18 pS
$k_{\text{PFK}}^{\text{F6P}}$	50 mM	k_{hyd}	2.34×10^{-2} s^{-1}	$k_{K(Ca)}^{Ca}$	0.5 μM
$k_{\text{PFK}}^{\text{FBP}}$	1 μM	$k_{hyd,bas}$	8.1×10^{-3} s^{-1}	$h_{K(Ca)}^{Ca}$	2
$k_{\text{PFK}-C}^{\text{FBP}}$	10 μM	q_1	0	$g_{K(\text{ATP})}$	2960 pS
$k_{\text{PFK}}^{\text{ATP}}$	0.25 μM	q_2	12.5 mM	kdd	17 mM
$k_{\text{PFK}}^{\text{FBP}}$	10 μM	q_3	5 μM/s	ktd	26 mM
f_{AMP}	0.02	ψ_m	164 mV	ktt	1 mM
f_{FBP}	0.2	$Vol_{m:c}$	0.07	C_m	5300 fF
f_{MT}	20	$F/(RT)$	0.04 mV	k_{PMCA}	41 s^{-1}
f_{BT}	20	$k_{\text{Perceval}}^{A_c}$	1 mM	$k_{\text{ER},in}$	83 s^{-1}
f_{ATP}	20	V_{Ca}	25 mV	$k_{\text{ER},out}$	4.14×10^{-2} s^{-1}
$k_{\text{PDH}}^{Ca_m}$	0.1 μM	V_K	-75 mV	k_{cyt}^{Ca}	9×10^{-3}
$k_{\text{PK}}^{\text{FBP}}$	2 μM	$g_{Ca(V)}$	180 pS	f_{ER}^{Ca}	0.01
k_{Ca}	5	$v_{Ca(V)}$	-20 mV	$Vol_{cyt:\text{ER}}$	26.96

Table 2: Parameter values for the model simulations in Fig. 2-7 unless otherwise specified.