Coupled Oscillations of Calcium and IP3: Identification of Feedback Loops

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Frequency-modulated Ca$^{2+}$ oscillations and control of metabolism in hepatocytes
Hormone

Neurotransmitter

Antigen

Phospholipase C (PLC)

$\text{PIP}_2 \rightarrow \text{IP}_3 \rightarrow \text{DAG}$

$\text{Ca(ER)} \leftrightarrow \text{Ca(cyt)}$

Calcium oscillator

Hormone

Neurotransmitter

Antigen

Phospholipase C (PLC)

$\text{PIP}_2 \rightarrow \text{IP}_3 \rightarrow \text{DAG}$

$\text{IP}_3$ oscillator

$\text{Ca(ER)} \leftrightarrow \text{Ca(cyt)}$

Ca elevates IP3
Haratoonian et al. (1991)
Venance et al. (1997)

Models for Ca/IP3 wave propagation
Höfer, Venance and Giaume (2002)
Dupont and Dummollard (2004)
Wagner et al. (2004)

Models with IP3 oscillations
Meyer and Stryer (1988)
Cuthbertson and Chay (1991)
Kummer et al. (2000)
Dupont and Erneux (1997)
Dupont et al. (2003)

Experiment: IP3/PIP2 oscillate
Hirose et al. (1999)
Nash et al. (2000)
Young et al. (2003)
Thore et al. (2004)

Is dynamic IP3 essential for the calcium oscillator?
3 modes of intercellular signaling

![Graph and images illustrating different modes of intercellular signaling.](image-url)
Hormone

Neurotransmitter

Antigen

Phospholipase C (PLC)

Ca\textsubscript{ER}

Ca\textsubscript{cyt}

PIP\textsubscript{2}

DAG

+/-

Ca\textsubscript{ER} \leftrightarrow Ca\textsubscript{cyt}
Slowing IP3 turnover with a buffer protein

\[
\frac{d[IP_3]}{dt} = \frac{1}{\tau_p} \left( V_{\text{prod}} - V_{\text{deg}} \right)
\]

\[
\tau_p = \frac{1}{k_p} \left( 1 + \frac{K_d B_r}{(K_d + [IP_3])^2} \right)
\]
Response to IP3 buffer in hepatocytes

How are IP3 oscillations mediated?
Do they serve a function?
Negative and positive feedbacks of calcium on IP3
Ca\textsuperscript{2+} activation of PLC

\[
\frac{dp}{dt} = \frac{1}{\tau_p} \left[ v_{PLC,1} + v_{PLC,2} \frac{c^2}{K_{PLC}^2 + c^2} - p \right]
\]

\[
\frac{dc}{dt} = \frac{1}{\tau_c} \left[ \frac{(rpc)^3}{(K_p + p)^3(K_a + c)^3} + k_2 \right] \left[ c_{ER} - c \right] - v_S \frac{c^2}{K_S^2 + c^2}
\]

\[
\frac{dr}{dt} = \frac{1}{\tau_r} \left[ 1 - (1 + c/K_i)r \right]
\]

\[W_c c + W_{ER} c_{ER} = n_{tot}\]
Ca\(^{2+}\) activation IP₃ 3-kinase

\[
\frac{dp}{dt} = \frac{1}{\tau_p} \left[ v_{PLC,1} - \left( 1 - \eta + \eta \frac{c^2}{K_{3K}^2 + c^2} \right) p \right], \quad 0 \leq \eta \leq 1
\]

Ca activation

\[
\frac{dc}{dt} = \frac{1}{\tau_c} \left[ \frac{(rpc)^3}{(K_p + p)^3(K_a + c)^3} + k_2 \right] \left( c_{ER} - c \right) - v_S \frac{c^2}{K_S^2 + c^2}
\]

\[
\frac{dr}{dt} = \frac{1}{\tau_r} \left[ 1 - (1 + c/K_i) r \right]
\]

\[W_c \, c + W_{ER} \, c_{ER} = n_{tot}\]
Feedbacks support frequency encoding of hormone dose.

**A** Positive feedback

**B** Negative feedback

With Ca\(^{2+}\) PM fluxes
Positive feedback

Negative feedback

[Graphs showing positive and negative feedback with concentrations over time]
Period control

\[ C_i^T = \frac{\partial \ln T}{\partial \ln \tau_i} \]

A. Positive feedback

![Graph showing control coefficients over period (s)]

B. Negative feedback

![Graph showing control coefficients over period (s)]

C. Additional graph

With Ca\textsuperscript{2+}

PM fluxes
Sensitivity to IP3 turnover differs

Positive feedback

Negative feedback

Ca\(^{2+}\) Amplitude (µM)

\(V_{PLC} \times \tau_p (\mu M)\)

Agonist stimulus

Range of oscillations for fast, intermediate, slow IP\(_3\) turnover
**IP$_3$ buffer affects Ca$^{2+}$ oscillations differently in the positive and negative feedback models**

Low IP$_3$ buffer

High IP$_3$ buffer
Complex buffer effects

A

B

C

Control (□)

IP$_3$ buffer (III, □)

IP$_3$ buffer (IV, ●)

[IP$_3$ buffer] (μM)

$V_{PLC}$ (μM/s)

[Ca$^{2+}$] (μM)

Time (s)

Control (○)

Time (s)
Experiment 3 – CHO cells

Model (+ve feedback, strong PM fluxes)

**ATP [µM]**

- EGFP
- LBD (1.5 µM)
- LBD (15 µM)
- LBD (30 µM)

**800 nM [Ca²⁺]**

[Graphs showing calcium oscillations with different conditions and concentrations.]

Control

- [IP₃ buffer] 1.5 µM
- [IP₃ buffer] 15 µM
- [IP₃ buffer] 30 µM

**[Ca²⁺] (µM)**

- Time (s)
Rate of calcium rise depends on IP3 buffer