Mathematical Model of Metabolic Oscillations in Pancreatic β-Cells

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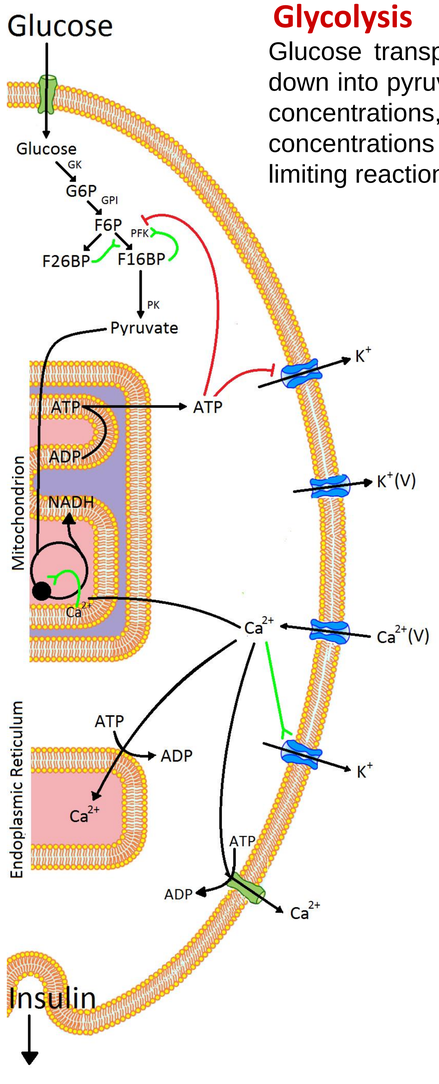
Overview

- Pancreatic islets are primarily composed of β-cells, which secrete insulin in response to elevated plasma glucose.
- Multiple signaling pathways, including glycolysis, oxidative phosphorylation, and transmembrane ion currents, regulate the secretion signal. (ref. 1)



Glycolysis

Glucose transported into cytosol is broken down into pyruvate. At intermediate glucose concentrations, oscillations in metabolite concentrations are introduced by a rate-limiting reaction.

Oxidative Phosphorylation

Pyruvate transported into mitochondria feeds the citric acid cycle to charge carriers including NADH. The mitochondrial electron transport chain, utilizing NADH, establishes an electrochemical gradient to power ATP production and transport into the cytosol.

Membrane Ion Channels

At low glucose, ion channels hold the cell membrane at a resting potential of about -60 mV. Glucose-induced rise in cytosolic [ATP]/[ADP] inhibits outward ATP-sensitive K^+ channels to depolarize the membrane. When depolarized above threshold, voltage-activated channels successively conduct Ca^{2+} and K^+ to and from the cytosol in an electric burst.

Ca^{2+} Signaling

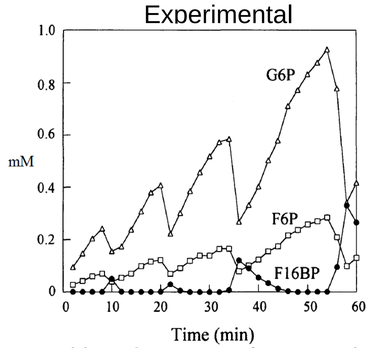
During the active phase, Ca^{2+} participates in several pathways. It promotes insulin-vesicle fusion to the membrane for secretion, it activates citric acid cycle enzymes to meet the cell's energy demands, and it activates outward K^+ channels to gradually recover resting membrane potential.

Model Behavior

Metabolic Oscillations

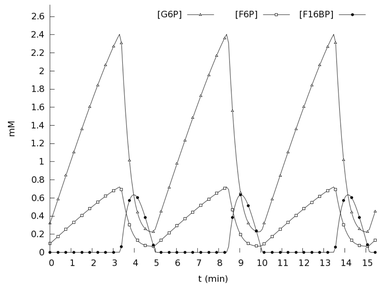
- The glycolytic reaction performed by the isoform of phosphofructokinase (PFK) present in β-cells is autocatalyzed to introduce oscillations in substrate [F6P] and product [F16BP]. (ref. 2)

Experimental



(data from muscle extract)

Model

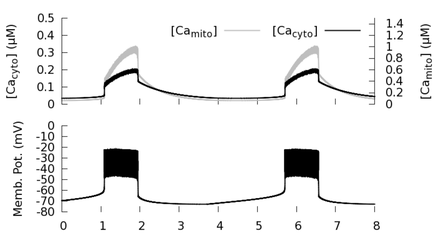


Electrical Oscillations

- In stimulatory glucose, electric bursts of membrane potential and transient increases in intracellular [Ca^{2+}] occur during the active phase, during which insulin is secreted. (ref. 1)

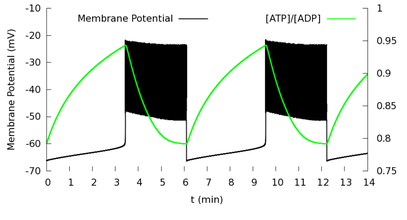
Experimental

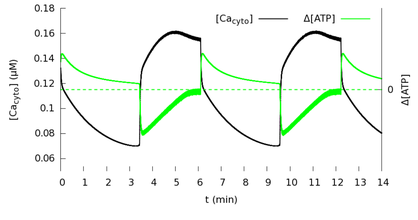
Model



Dual roles of ATP

- During the silent phase, glucose-induced increase in [ATP] /[ADP] depolarizes the membrane to initiate the active phase.
- During the active phase , Ca^{2+}-dependent utilization of ATP outpaces production.

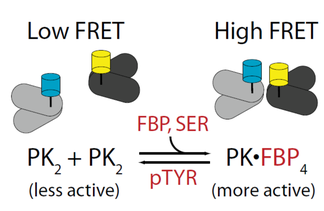


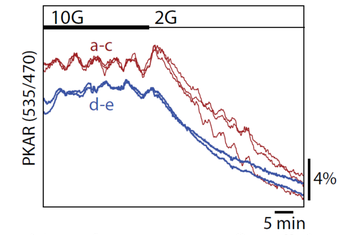


Application

Understanding Direct Measurement of Glycolysis

- Enzyme pyruvate kinase (PK) produces pyruvate in final glycolytic reaction, and is primarily activated as a tetramer by F16BP.
- FRET sensor "PK activity reporter (PKAR)" fluoresces proportional to [F16BP] when enzyme is tetramerized. (ref. 3)

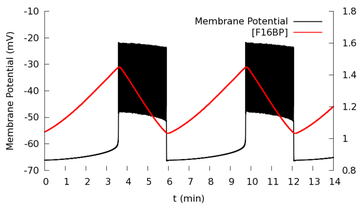


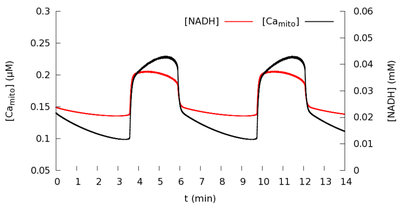


(data from mouse β-cells)

What is the role of glycolysis in regulating the secretion signal?

- During silent phase, a PFK-mediated rise in [F16BP] promotes ATP production to initiate the active phase.
- During the active phase, mitochondrial Ca^{2+} influx promotes oxidative phosphorylation to decrease lower glycolytic metabolites and attenuate PFK autocatalysis.





Conclusion

- We used a mathematical model of signals coupled to insulin secretion in β-cells to show that mitochondria energized by glucose-induced Ca^{2+} influx may compete with PFK autocatalysis to shape glycolytic oscillations.

References

1. Richard Bertram, Arthur Sherman, and Leslie S. Satin. "Electrical Bursting, Calcium Oscillations, and Synchronization of Pancreatic Islets." The Islets of Langerhans. Springer Netherlands, 2010. 261-279.
2. Tornheim, Keith. "Are metabolic oscillations responsible for normal oscillatory insulin secretion?." *Diabetes* 46.9 (1997): 1375-1380.Min Zhang, Paula Goforth, Richard Bertram, Arthur Sherman, and Leslie Satin. The Ca^{2+} Dynamics of Isolated Mouse β-Cells and Islets: Implications for Mathematical Models. Biophysical Journal, 84(5):2852-2870, 2003.
3. Matthew J. Merrins, Aaron R. Van Dyke, Anna K. Mapp, Mark A. Rizzo, and Leslie S. Satin. Direct Measurements of Oscillatory Glycolysis in Pancreatic β-cells Using Novel Fluorescence Resonance Energy Transfer (FRET) Biosensors for Pyruvate Kinase-M2 Activity. Journal of Biological Chemistry, 288(46):33312-33322, 2013.