Effects of Hidden Calcium Pools on Cell Electrical Activity

Inferring the Unseen

Arthur Sherman
National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases
Bethesda, MD 20892
asherman@nih.gov

Leslie Satin
Department of Pharmacology and Toxicology
Medical College of Virginia at Virginia Commonwealth University
Richmond, VA 23298-0001
lsatin@hsc.vcu.edu

Richard Bertram
Department of Mathematics and Institute of Molecular Biophysics
Florida State University
Tallahassee, FL 32306
bertram@sb.fsu.edu

ABSTRACT

Calcium is a critical activator of secretion from endocrine cells and neurons, and also regulates its own entry through negative feedback on ion channels. Using pancreatic β-cells as a model system, we use differential equation models to study the involvement of cytosolic calcium, which is readily measured, as well as calcium in internal stores, such as the endoplasmic reticulum (ER), which is not easily measured. We infer from detailed measurements of currents through calcium-activated potassium channels the existence of yet another compartment, which lies in close proximity to both a portion of the ER and the plasma membrane.

Rhythmic bursts of electrical activity are central to the regulated transduction of plasma glucose levels to insulin secretion by β-cells. These oscillations occur with periods ranging from seconds to minutes, the latter approaching the scale of oscillations of insulin and glucose in the plasma, whose disappearance foreshadows the development of Type II diabetes. Loss of the first phase of insulin secretion when glucose is rapidly raised from basal levels is another well-established predictor of Type II diabetes and a correlate of diabetes in β-cell insulin-receptor knockout mice. This is possibly related to the initial transient of electrical activity seen when glucose is raised above the threshold for oscillations in vitro. The mechanisms of oscillation are complex and have eluded a final determination, but there is wide agreement that negative feedback processes, which slowly switch action potential firing and Ca^{2+} entry on and off, are involved. One of the first candidate mechanisms considered was activation of K^+ channels by the rise in cytosolic Ca^{2+} itself. This hypothesis, originally proposed by Atwater and Rojas [1], fell into disfavor but has received renewed attention with the isolation by Rorsman and colleagues of a Ca^{2+}-sensitive K^+ conductance, K_{slow}, that slowly rose and fell in response to voltage-clamp stimuli that simulated the natural burst waveform of the cells [3].

We have confirmed the existence of this channel in mouse β-cells and islets and HIT cells with a similar protocol and ascertained that:

1. K_{slow} is abolished by thapsigargin (Tg), which depletes the ER by blocking the SERCA pump.
2. Insulin blocks K_{slow} in a manner indistinguishable from Tg.
3. Raising glucose partially inhibits K_{slow}.

The action of insulin suggests a novel mechanism for paracrine communication in islets, while the action of glucose suggests the K_{slow} may contribute to non-KATP-dependent glucose sensitivity, such as observed in SUR1 knockout mice, an animal model for familial hyperinsulinism. We hypothesized that K_{slow} is activated by Ca^{2+} released from the ER into a submembrane space (subspace), which generates local Ca^{2+} concentrations significantly greater than those in the bulk cytosol. Depletion of stores turns off K_{slow} by collapsing this gradient. We have tested this hypothesis by constructing a mathematical model that can quantitatively account for the detailed response of K_{slow} to store depletion, whereas simpler models incorporating the ER but not a subspace fail. The model also produces oscillations of membrane potential and cytosolic Ca^{2+} on the full range of observed timescales, from seconds to minutes (cf. [2]). Finally, transient suppression of K_{slow} as the ER fills provides a new candidate mechanism for the first phase of electrical activity in vitro.

ADDITIONAL AUTHORS

Paula Goforth (The Satin Group, email address: `pgoforth@hsc.vcu.edu`) and Min Zhang (The Satin Group, email address: `mzhang15@hotmail.com`).

REFERENCES

[1] I. Atwater, C. M. Dawson, A. Scott, G. Eddlestone, and E. Rojas. The nature of the oscillatory behavior in electrical activity for pancreatic β-cell. *Horm. Metab. Res. Suppl. 1980*, Suppl. 10:100–107, 1980.

[2] R. Bertram, J. Previte, A. Sherman, T. A. Kinard, and L. S. Satin. The phantom burster model for pancreatic β-cells. *Biophys. J.*, 207:513–530, 2000.

[3] S. O. Göpel, T. Kanno, S. Barg, L. Eliasson, J. Galvanovskis, E. Renström, and P. Rorsman. Activation of Ca^{2+}-dependent K^+ channels contributes to rhythmic firing of action potentials in mouse pancreatic β cells. *J. Gen. Physiol.*, 114:759–769, 1999.