Importance of Islet Cell Synchrony for the β-Cell Glucose Response

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Islets of Langerhans are small organs consisting of several thousand endocrine cells, mainly insulin secreting β-cells, and are found scattered throughout the pancreas. The islet is considered the fundamental functional unit of insulin secretion. While the various cellular components involved in stimulus-secretion coupling (ionic channels, calcium fluxes, second messenger molecules, fusion proteins, etc.) participate in glucose sensing and insulin secretion, the organized electrical activity (i.e., bursting) and normal insulin response to glucose (i.e., an S-shaped dose response) are only observed from clustered β-cells or intact islets.

It is then incumbent upon us to determine how the β-cells of the islet communicate with each other (and with the other cell types) to generate a coordinated response. The natural answer is conduction of current and transfer of small molecules through gap junctions. The presence of gap junctions between β-cells is undeniable; the issue is the strength and density of connections. The pages of this journal have conveyed some of the key experimental and theoretical work on junctions. Most recently, Perez et al. (1) measured junctional conductance between β-cells to be variable but averaging 200 pS/cell interface. About 65% of dissociated pairs from islets were connected. Smolen et al. (2) found that this was adequate to mediate synchronized bursting in model islets, even when the cells were very heterogeneous and most of them were not bursting on their own. However, in a more pessimistic report, Meda et al. (3) found only 20% of cell pairs to be connected, clearly not enough for synchrony. Dye transfer experiments in intact islets also indicate limited domains of connectivity. Furthermore, electrical activity measured between two cells in an islet and separated by about 300 μm (approximately 30 cells) is not perfectly synchronous; one cell's burst of electrical activity lags behind the other's by about 2 s, suggesting restricted electrical coupling (4).

In this issue we have a theoretical study by Stokes and Rinzel (5) to assess an alternative communication medium —ionic diffusion in the restricted intercellular space. That work was motivated by experiments showing that extracellular K^+ oscillates during bursting (6). Just as the experimentalist commonly depolarizes cells by applying K^+ exogenously, cells can depolarize each other by means of the K^+ they naturally release during a burst of action potentials. Tuckwell and Miura (7) had previously proposed such a mechanism for cortical spreading depression waves.

Stokes and Rinzel show that individually bursting units can be synchronized quickly (within a few seconds) solely by K^+ effects. In their picture the outer cells, assumed to be in contact with a constant K^+ bath, burst with the highest frequency and act as pacemakers entraining the interior cells. The model is supported by experiments and simulations showing that islets can be entrained either faster or slower than their natural frequency by external application of K^+ pulses. K^+ diffusion by itself is probably not enough to explain all of islet synchronization, especially in the face of channel noise and cell heterogeneity, but it is likely to be part of the answer.

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Received for publication and in final form 9 June 1993.

0006-3495/93/08/565/01 $2.00