The role of glucose-dependent mobilization and priming of insulin granules in insulin release

I. Johanna Stamper[1,2], Xujing Wang[1,2]

Short Abstract — **In this study we develop and analyze a mathematical model of glucose-induced insulin secretion from pancreatic islet beta-cells. We assume a fully homogeneous beta-cell population, and that insulin granules reside in five different pools that primarily include mobilized, primed, docked, and fused. We show that the model reproduces the characteristic insulin release observed in multiple experimental systems, and assumption of heterogeneous beta-cell response is not necessary, In addition to the glucose dependent fusion rate of insulin granules, we found that their mobilization and priming from the reserve are also critical limiting factors for the total insulin release.**

Keywords **—insulin secretion, insulin granule dynamics, multiple pool, β-cells, diabetes**

I. Purpose

The goal of this study is to investigate the critical rate limiting factors in glucose stimulated insulin release. Insulin is the primary regulating hormone of blood glucose, and is produced and released by the pancreatic islet beta cells. A normal beta cell contains an excessive amount of insulin granule, and only a small amount is ever released (~5%). The intra-beta cell insulin granule trafficking is not well understood. Specifically, it is not clear why the vast reserve cannot be readily tapped into to compensate for increased demand under pathological conditions such as diabetes.

II. Model and Results

A. The Model

In our model we divide the insulin granules into five subgroups depending on their properties: mobilized unprimed granules, $M_u(t)$; mobilized primed granules, $M_p(t)$; docked unprimed granules, $D_u(t)$; docked primed granules, $D_p(t)$; and fused granules, $F(t)$. The model design, variables and parameters are given in Figure 1. The processes are assumed to be glucose dose-dependent. We assume that the pool of release-ready granules (RRP) consists of the docked and the mobilized, i.e. RRP=$M_p(t)+D_p(t)$.

B. Results

Our model reproduces the characteristic insulin release observed in multiple experimental systems, including perfused pancreata and isolated islets of rodent or human origin, under several different glucose administration protocols including the single step, stair case, and negative spike experiments. In addition, it reveled that that first-phase insulin secretion depends on rapid depletion of the primed, release-ready granule pools, while the second phase relies on granule mobilization from the reserve. Moreover, newcomers have the potential to contribute significantly to the second-phase.

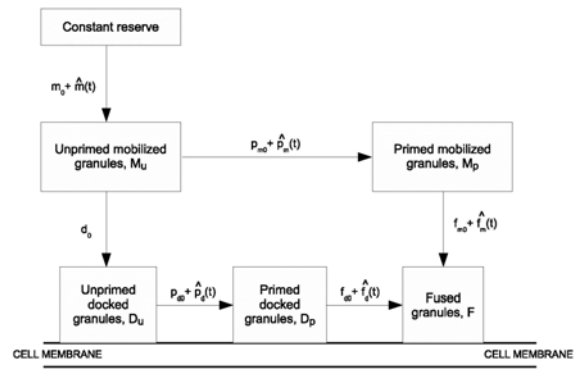

Figure 1. Schematic diagram of our model.

III. Conclusion

Our model assumed homogenous beta cell population, and is able to reproduce multiple experimental systems including the staircase experiment which, largely due to previous mathematical modeling [1,2], has been regarded as an indicator of heterogeneous β-cell recruitment. Although heterogeneity has been observed in the glucose sensitivity of individual β-cells, it is also recognized their crosstalk within intact islets, alters their individual responses [3,4]. It was found that recruitment of islet β-cells occurs over a narrower glucose range than that of individual cells [3,5]. In addition, our model suggests that the strength of insulin granule mobilization and priming are critical rate limiting factors for insulin release during the second phase, and hence for the total insulin release.

References

[1] Pedersen, M.G., A. Corradin, G.M. Toffolo, and C. Cobelli, *A subcellular model of glucose-stimulated pancreatic insulin secretion.* Philos Transact A Math Phys Eng Sci, 2008. **366**(1880): p. 3525-43.

[2] Grodsky, G.M., *A threshold distribution hypothesis for packet storage of insulin and its mathematical modeling.* J Clin Invest, 1972. **51**(8): p. 2047-59.

[3] Jonkers, F.C. and J.C. Henquin, *Measurements of cytoplasmic Ca2+ in islet cell clusters show that glucose rapidly recruits beta-cells and gradually increases the individual cell response.* Diabetes, 2001. **50**(3): p. 540-50.

[4] Nittala, A., S. Ghosh, and X. Wang, *Investigating the Role of Islet Cytoarchitecture in Its Oscillation Using a New beta-Cell Cluster Model.* PLoS ONE, 2007. **2**(10): p. e983.

[5] Speier, S., et. al., *Cx36-mediated coupling reduces beta-cell heterogeneity, confines the stimulating glucose concentration range, and affects insulin release kinetics.* Diabetes, 2007. **56**(4): p. 1078-86.

[1]Department of Physics, University of Alabama at Birmingham, Birmingham, AL, 35294. E-mail: xujingw@uab.edu

[2]The Comprehensive Diabetes Center, University of Alabama at Birmingham, Birmingham, AL, 35294