The role of glucose-dependent mobilization and priming of insulin granules in the biphasic insulin secretion

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Insulin is the primary regulating hormone of blood glucose, and is produced and release by the pancreatic islet beta cells. A normal beta cell contains an excessive amount of insulin granules, and only a small proportion is ever used. This is even true even under pathological conditions such as diabetes, where demand for insulin is increased but not adequately compensated. The rate limiting steps in insulin secretion, and why the diabetics cannot tap into the vast insulin reserve inside beta cells, are not well understood.

In this study we develop and analyze a mathematical model of glucose-induced insulin secretion from pancreatic islet beta-cells. We assume that insulin granules reside in different pools; also, consistent with recent experimental observations, our model accounts for the fusion of newcomer granules that are not pre-docked at the plasma membrane. In response to a single step increase in glucose concentration, our model reproduces the characteristic biphasic insulin release observed in multiple experimental systems, including perfused pancreata and isolated islets of rodent or human origin.

From our model analysis we note 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. When the glucose protocol consists of multiple changes in sequence (a so-called glucose staircase), our model predicts insulin spikes of increasing height as seen experimentally. In contrast to previous mathematical models, in which the staircase experiment was reproduced by assuming heterogeneous beta-cell activation, we assume a fully homogeneous beta-cells population. In our model the increasing spikes in insulin secretion instead stem from the glucose-dependent increase in the fusion rate of insulin granules at the plasma membrane of single beta-cells. In light of experimental data indicating limited heterogeneous activation when beta-cells are arranged within islets, our findings suggest that a graded, dose-dependent cell response to glucose may contribute to insulin secretion patterns observed in multiple experiments, and thus regulate *in vivo* insulin release.