Multiscale Modeling of Insulin Secretion

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***Abstract*—Insulin secretion from pancreatic beta cells is a fundamental physiological process, and its impairment plays a pivotal role in the development of diabetes. Mathematical modeling of insulin secretion has a long history, both on the level of the entire body and on the cellular and subcellular scale. However, little direct communication between these disparate scales has been included in mathematical models so far. Recently, we have proposed a minimal model for the incretin effect by which the gut hormone glucagon-like peptide 1 (GLP-1) enhances insulin secretion. To understand how this model couples to cellular events, we use a previously published mechanistic model of insulin secretion, and show mathematically that induction of glucose competence in beta cells by GLP-1 can underlie derivative control by GLP-1.**

***Index Terms*—Derivative control, glucagon-like peptide 1 (GLP-1), incretins, insulin granules, threshold distribution.**

I. Introduction

INSULIN is a hormone secreted from beta cells in the endocrine pancreas to counteract elevated plasma glucose levels by inhibiting hepatic glucose output and stimulating glucose uptake by muscle and adipose tissues. It is now generally recognized that impaired insulin release contributes to the onset of diabetes [1]. The importance of defective insulin secretion is highlighted by the fact that most genes associated with diabetes are related to beta-cell function [2].

Glucose-stimulated insulin secretion is a complex process, where glucose is transported into the beta cells to undergo metabolism, which increases adenosine triphosphate (ATP) levels. The raised ATP-to-adenosine diphosphate ratio closes ATP-sensitive potassium K(ATP) channels, which allows a background leak current to depolarize the cell membrane. The depolarization causes electrical activity, which involves voltage-sensitive Ca^{2+} channels, and the resulting Ca^{2+} influx triggers exocytosis of insulin-containing secretory granules and insulin release (see Fig. 1, left) [3].

Mathematical modeling of insulin secretion has been performed on several levels to aid in interpretation of data (see Fig. 1). On a macroscopic level, minimal models of insulin secretion [4] has been used to obtain a deeper insight from data of clinical glucose tolerance tests, notably the intravenous glucose tolerance test [5] and the oral glucose tolerance test (OGTT) [6]. In particular, such models have shown that glucose exhibits "derivative control" of insulin secretion, i.e., the rate-of-change dG/dt of the glucose concentration G can control pancreatic insulin release (see Fig. 1, right) [7]. Such a secretion model has also been used to simulate a virtual population of healthy, prediabetic or type 2 diabetic subjects by inclusion in a larger model including other organs, and where parameters are allowed to vary to mimic natural variation between subjects [8].

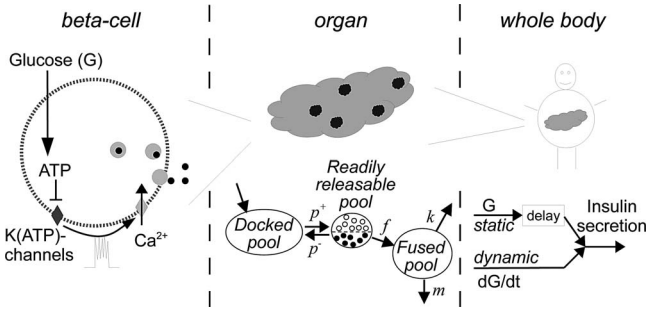

Fig. 1. Overview of different levels of insulin secretion and corresponding models. (Left) Consensus pathway of glucose-stimulated insulin secretion from pancreatic beta cells. (Middle) Beta cells are located in the pancreatic islets, which are scattered through out the pancreas. An overview of the model from [10] is shown. (Right) *In vivo* clinical data are favorably analyzed with minimal models. An overview of the OGTT model from [6] is shown.

Other more detailed models have studied overall *in vitro* insulin secretion from perfused pancreases [9], [10]. On a subcellular levels, models investigating various aspects of beta-cell secretory granule dynamics have been published recently [11]–[14], while modeling of electrical activity in beta cells has a longer history [15], [16]. These models on the organ and cellular level have been based on data mostly from rodents, and the first model of electrical activity in human beta cells appeared only recently [17].

Linking between these different levels of insulin secretion has mainly been done using ad hoc simplifications. For example, complex bursting electrical activity can be replaced by square pulses [13], or all cellular processes from glucose uptake via electrical activity to exocytosis of insulin-containing granules can be reduced to a direct effect of glucose on secretion [9], [10]. More rigorous coupling between organ scale and minimal models of secretion has been recently performed using mathematical simplifications [18], which explained how derivative control of insulin secretion can appear from the assumption that single beta cells become active at different glucose concentrations [10], [19]. On the molecular level, the control of such a glucose threshold for electrical activity by different ion channels in human beta cells has recently been investigated using a mathematical model [17].

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Glucagon-like peptide 1 (GLP-1) is a hormone secreted from the intestinal L-cells in response to meal ingestion, and affects several important physiological mechanisms involved in metabolic control [20]. Of particular interest here, GLP-1 causes a strong potentiation, denoted as the incretin effect, of glucose-stimulated insulin secretion by several actions on the beta cells [20], [21]. Recently, the first mathematical model of GLP-1 potentiated insulin secretion has been developed and validated against clinical measurements [22]. This model included both direct and dynamic control of GLP-1 on insulin release, i.e., both the GLP-1 plasma concentration and its rate of change modulated the secretion rate.

Here, we show that dynamic control by GLP-1 can be explained by data suggesting that GLP-1 shifts the glucose threshold of activity in beta cells. Thus, we suggest that the control of glucose-stimulated insulin secretion by the rate of change of GLP-1 is related to the activity threshold of beta cells, in line with the explanation for the appearance of dynamic control of insulin secretion by glucose [9], [18]. Modeling of electrical activity in human cells [17] have shown that such a shift in threshold can be explained by effects of GLP-1 on a leak current [23] or on K(ATP) channels [24]. Modeling on multiple scales, from ion channels to *in vivo* pancreatic secretion, therefore, gives a coherent picture of one of the mechanisms of the incretin effect of GLP-1 on insulin secretion, and the *in vivo* effect can be linked to testable predictions on the molecular level.

II. Results

GLP-1 has several direct effects on beta cells [21], and has in particular been shown to render otherwise electrically silent beta cells active [23]–[25]. This effect can be attributed to inhibition by GLP-1 of K(ATP) channels [21], [24], [25]. In addition, GLP-1 also stimulates a nonselective cation leak current, which would left shift the glucose threshold for electrical activity [23]. Mathematical modeling of the electrophysiology of human beta cells has supported that either inhibition of K(ATP) channels or activation of a leak current would left shift the threshold for activity [17].

No matter what the main mechanism by which GLP-1 activates otherwise silent beta cells, we will now move up a level and investigate the result of this factual activation. Of course, other effects of GLP-1 on insulin secretion beside a shift of the threshold for activity should be considered for a full picture of the incretin effect, but we will here limit ourselves to study whether a threshold shift can explain derivative control of GPL-1 on insulin secretion [22]. Once the beta cells are active, GLP-1 has only modest effects on Ca^{2+} influx, but enhances insulin secretion greatly, likely due to cAMP-mediated signaling through PKA and Epac2 to potentiate insulin granule exocytosis [3], [20], [21], [25].

Our subcellular model [10] describes the dynamics of granule pools in the entire pancreatic population of beta cells (see Fig. 1, middle). Granules mobilize from a reserve pool to a pool of "docked" granules at the plasma membrane. The granules can mature further (priming) to gain release competence and enter the readily releasable pool (RRP). Calcium influx then triggers exocytosis and insulin release from the RRP. The glucose-dependent increase in the number of cells showing a calcium signal [19] was included by distinguishing between readily releasable granules in silent and active cells. Therefore, the RRP is heterogeneous in the sense that only granules residing in cells with a threshold for calcium activity below the ambient glucose concentration are allowed to fuse. The RRP is described by a time-varying density function $h(g,t)$, representing the amount of insulin in the RRP in beta cells with a threshold between g and $g+dg$. The fraction of beta cells with threshold g is modeled by the time-independent function $\phi(g)$, whereas the cumulative function $\Phi(G)=\int_0^G \phi(g)dg$ describes the fraction of active cells at G, i.e., cells with threshold below G. The priming rate is p^+, and granules are assumed to lose exocytotic capacity at rate p^-. Moreover, if the granule is in a active beta cell, i.e., a cell with a threshold below the glucose concentration, it will fuse with rate f.

The over basal secretion rate can be expressed as $\Delta\mathrm{SR}(t)=\mathrm{SR}(t)-\mathrm{SR}_b=mF(t)$, where SR_b is the basal secretion, m is the rate constant of release, and F is the size of the fused pool, which follows

$$\frac{dF}{dt}=fH(G,t)-(m+\kappa)F(t) \tag{1}$$

where f is the rate constant of fusion, κ is the kiss-and-run rate, and $H(G)=\int_0^G h(g)dg$ represents the amount of insulin in the RRP in cells with a threshold below G. For further details of the model, we refer to the original article [10].

We assume that GLP-1 shift the threshold linearly, so that cells with threshold below $G+\gamma\,\mathrm{GLP1}$ are active at the glucose concentration G when GLP-1 is present at concentration GLP1, i.e., otherwise silent cells with threshold between G and $G+\gamma\,\mathrm{GLP1}=\hat{G}$ become active. Then the amount of releasable insulin in active cells is given by

$$H(\hat{G})=\int_0^{G+\gamma\mathrm{GLP1}} h(g,t)dg=\int_0^{\hat{G}} h(g,t)dg \tag{2}$$

and as in [18], we differentiate to get

$$\begin{aligned}\frac{dH(\hat{G})}{dt}=&-(f+p^-)H(\hat{G},t)+p^+D(t)\Phi(\hat{G})\\&+h(\hat{G},t)\frac{dG}{dt}+\gamma h(\hat{G},t)\frac{d\mathrm{GLP1}}{dt}.\end{aligned} \tag{3}$$

As in [18], we assume equilibrium in (1) and (3) and obtain

$$\Delta\mathrm{SR}=C\left(p^+D(t)\Phi(\hat{G})+h(\hat{G},t)\frac{dG}{dt}+\gamma h(\hat{G},t)\frac{d\mathrm{GLP1}}{dt}\right) \tag{4}$$

with $C=[m/(m+\kappa)][f/(f+p^-)]$. Thus, ΔSR is the sum of static secretion $\mathrm{SR}_s(\hat{G})=Cp^+D(t)\Phi(\hat{G})$, dynamic secretion $\mathrm{SR}_d(\hat{G})=Ch(\hat{G},t)\frac{dG}{dt}$ and an additional term reflecting dynamic control by GLP-1, $\mathrm{SR}_{d,\mathrm{GLP_1}}(\hat{G})=C\gamma h(\hat{G},t)\frac{d\mathrm{GLP_1}}{dt}$, compared with [6] and [18].

Dalla Man *et al.* [22] suggested that GLP-1 modified the secretion rate multiplicatively, so that the secretion rate was

given by

$$\Delta\mathrm{SR} = (\mathrm{SR}_d + \mathrm{SR}_s)\left(1 + a\mathrm{GLP1} + b\max\left[0, \frac{d\mathrm{GLP1}}{dt}\right]\right) \tag{5}$$

but noted that the model had been validated only when G was approximately constant, and, therefore, that a model where GLP-1 modified the static secretion term only performed as well as the model given by (5). On the other hand, in [26], we found that the incretin effect stimulated both dynamic and static secretion.

By a quasi-equilibrium assumption, it can be shown that the function h satisfies approximately [18]

$$h(\hat{G}, t) = \begin{cases} p^+ D(t)\phi(\hat{G})/p^- & \text{for } \dfrac{d\hat{G}}{dt} > 0 \\ p^+ D(t)\phi(G)/(p^- + f) & \text{otherwise} \end{cases} \tag{6}$$

so that if G is near constant, then a significant derivative control by GLP-1 is obtained only when $\frac{d\mathrm{GLP_1}}{dt} > 0$, since f is much larger than p^+ and p^-. This explains why only increasing GLP-1 levels modify ΔSR in the last term of (5).

Moreover, (6) implies that we can write (4) as

$$\Delta\mathrm{SR} = \mathrm{SR}_d(\hat{G}) + \mathrm{SR}_s(\hat{G})\left\{1 + \frac{\gamma\phi(\hat{G})}{p^-\Phi(\hat{G})}\max\left[0, \frac{d\mathrm{GLP1}}{dt}\right]\right\} \tag{7}$$

and when G is approximately constant, first-order Taylor expansions yield

$$\Delta\mathrm{SR} = \mathrm{SR}_d(G)(1 + c\,\mathrm{GLP1}) + \mathrm{SR}_s(G) \times \left\{1 + a\,\mathrm{GLP1} + b\,(1 + c\,\mathrm{GLP1})\max\left[0, \frac{d\mathrm{GLP1}}{dt}\right]\right\} \tag{8}$$

with $a = \gamma\phi(G)/\Phi(G)$, $b = a/p^-$, and $c = \gamma\frac{d\phi}{dg}(G)/\phi(G)$. Note that (8) is in excellent agreement with [22] if the derivative control of GLP-1 is on the static secretion term only, compared with (5). Also, a stimulation of dynamic secretion is apparent in (8), which in combination with other effects of GLP-1 on beta cells, besides the shift in activation threshold [21], could underlie the incretin effect on SR_d found in [26].

III. Conclusion

Mathematical modeling of insulin secretion has been performed of several physiological levels from subcellular events to *in vivo* kinetics relevant for clinical studies. It is of natural interest to link these levels, for example, to help understand how molecular defects or pharmacological interventions influence human physiology, and vice versa, to obtain hints at which mechanisms are impaired in beta cells from clinical data.

A rigorous coupling between our subcellular model [10] and minimal models [6] has been performed recently [18]. Using the same techniques, we here showed how the incretin effect of GLP-1 on insulin secretion, as described in our recent model [22], can be linked to events of the cellular level by assuming that GLP-1 shifts the activity threshold to lower glucose concentrations, as has been found experimentally [23]–[25]. Future studies should also include effects of GLP-1 on exocytosis downstream of electrical activity and calcium influx [20], [21], [25]. To link to molecular events, modeling can also be of help in the interpretation of data as, e.g., shown in the investigation of the control of the activity threshold by leak and K(ATP) channels [17].

We would finally like to highlight the need for detailed models build on human data in order to make meaningful couplings to clinical data, which ultimately should help our understanding of the pathophysiology of the (human) disease diabetes.

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