Mathematical Biosciences 244 (2013) 69–81

Contents lists available at SciVerse ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

Review

Mathematical modeling of the glucose–insulin system: A review

Pasquale Palumbo [a], Susanne Ditlevsen [b,*], Alessandro Bertuzzi [c], Andrea De Gaetano [a]

[a] BioMatLab, IASI "A. Ruberti", National Council of Researches, UCSC Largo A. Gemelli 8, 00168 Rome, Italy
[b] Department of Mathematical Sciences, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark
[c] IASI "A. Ruberti", National Council of Researches, Viale Manzoni 30, 00185 Rome, Italy

ARTICLE INFO

Article history:
Received 3 December 2012
Received in revised form 10 May 2013
Accepted 16 May 2013
Available online 1 June 2013

Keywords:
Diabetes
Minimal Model
IVGTT and OGTT
Insulin secretion and oscillations
Euglycemic Hyperinsulinemic Clamp
Long-term diabetes

ABSTRACT

Mathematical modeling of the glucose–insulin feedback system is necessary to the understanding of the homeostatic control, to analyze experimental data, to identify and quantify relevant biophysical parameters, to design clinical trials and to evaluate diabetes prevention or disease modification therapies. Much work has been made over the last 30 years, and the time now seems ripe to provide a comprehensive review. The one here proposed is focused on the most important clinical/experimental tests performed to understand the mechanism of glucose homeostasis. The review proceeds from models of pancreatic insulin production, with a coarser/finer level of detail ranging over cellular and subcellular scales, to short-term organ/tissue models accounting for the intra-venous and the oral glucose tolerance tests as well as for the euglycemic hyperinsulinemic clamp, to total-body, long-term diabetes models aiming to represent disease progression in terms of β-cell population dynamics over a long period of years.

1. Introduction

The glucose–insulin system offers one of the clearest and simplest examples of homeostatic control in the organism. The level of glucose in blood needs to be kept within a narrow range. Since it represents the main metabolic substrate, or energy source, for brain tissue, abnormally low glucose concentrations give rise to anxiety, tremors, aggressiveness, obfuscation, coma and eventually death. On the other hand, excessive plasma glucose concentrations produce microvascular damages (notably in the retina and kidney) and neural damages, leading among others to blindness and chronic renal insufficiency. The way the body controls glycemia seems deceptively simple. Essentially a single hormone (insulin) is secreted by the β-cells of the pancreas in response to rising glucose concentrations (hyperglycemia). Insulin effects include increasing peripheral tissue glucose uptake (mainly by the muscle and fat tissues) and decreasing spontaneous glucose output by the liver. When insulin secretion by the pancreas is insufficient or absent, due to (autoimmune) destruction of β-cells, the clinical picture of Type 1 Diabetes Mellitus (T1DM) results; when insulin is secreted in normal, or supranormal amounts, but it is ineffective in lowering glycemia to normal levels, Type 2 Diabetes Mellitus (T2DM) is said to be present. A number of hormones contribute to rescuing the organism from hypoglycemia (adrenalin, glucagon, growth hormone, cortisol): however, since in clinical practice the situation of interest is normally inappropriately high glycemia, concentrating attention on the response to hyperglycemia by insulin seems justified, at least as a first modeling approach. We may therefore consider, as a first approximation, a simplified system in which a single metabolite (glucose) is controlled by a single hormone (insulin). This system will have to maintain glycemia in the absence of food intake, and will have to suppress hyperglycemia rapidly after meals, without incurring in dangerous hypoglycemias. We see therefore that the glucose–insulin system could be viewed, at least approximately, as a feedback control with a controller (the pancreas) and multiple effectors (muscle, liver, fat tissue), but where the only state variables of interest are glycemia and insulinemia.

The present review has the goal of highlighting the biomedical problem of the glucose–insulin homeostasis from a physiological and clinical viewpoint, then describing the main combined experimental-modeling tools which are currently employed in investigating the behavior of the control system in individuals or populations. The review is structured as follows. The next section focuses on one specific biological function played by the pancreas, the organ responsible for glucose homeostasis by means of glucose-stimulated insulin production. In this case the range of the available models for insulin release spans a subcellular (models dealing with the molecular mechanisms leading to the ejection of the insulin packet from a beta-cell), and a cellular/organ level (models treating the pancreas as a population of secretory units). In these cases the loop is often (but not always) closed with the action of remote organs and tissues (explaining the occurrence of

* Corresponding author. Tel.: +45 35320785.
E-mail address: susanne@math.ku.dk (S. Ditlevsen).

0025-5564/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.mbs.2013.05.006

sustained insulin oscillations, apparent in long-term clinical experiments). The time scale corresponding to these secretion phenomena is of milliseconds to seconds (or minutes in the case of potentiation).

Section 3 deals with glucose–insulin models aiming to describe glucose homeostasis from a top-down point of view, at the organ and tissue levels without getting too deep into the molecular/subcellular details (e.g. the ones related to insulin-dependent glucose uptake or to glucose–induced insulin production). These models describe the glucose/insulin dynamics from a phenomenological viewpoint, typically employ compartmental formalization and are strongly related to specific clinical protocols for which they provide information on "how good" are pancreatic insulin secretion and peripheral glucose uptake in the subject under investigation.

Finally, the last section addresses total-body models developed to offer the physician some glimpse on the possible long-term evolution of the disease Diabetes, depending on long-term (months to years) evolution of the beta-cell population and its replicating ability in the face of potential glucose toxicity. The following sections, therefore, cover multiple size and time scales, from subcellular and cellular phenomena of seconds, to organ/tissue functional interplay over minutes to hours, to cell replication and long-term total-body adaptation over months to years.

2. Insulin secretion and oscillations

Mathematical modeling of glucose-stimulated pancreatic insulin secretion is a challenging research topic that has involved much work in the last decades. Among the first references we find the pioneering work of Grodsky [37], who first distinguished a first phase of insulin release, due to the insulin packets immediately releasable as a consequence of a rapid increase in glycemia, from the second phase related to the potentiation effect that occurs during a sustained glucose stimulation. The models reported in Section 2.1 take place over a fine biological scale, detailing the subcellular mechanism (the insulin granule dynamics) that eventually determines insulin release from the β-cell. Phenomena at a subcellular scale could be invoked to explain the occurrence of sustained oscillations in pancreatic insulin release (the topic of Section 2.2): however the different kinds of oscillations may be better explained according to a coarser, larger scale population model of the secretory units, that is also able to reproduce a large collection of clinical experiments.

2.1. Insulin granule dynamics

Insulin granule trafficking in pancreatic β-cells has been investigated in recent years by using fluorescent proteins that are targeted to secretory granules and allow the real-time imaging of granules in living cells [70]. A β-cell contains 10,000–13,000 granules of diameter $\sim$350 nm, each containing $\sim$1.6 amol of insulin plus other polypeptides and smaller molecules. Most granules belong to a large "reserve pool", around 600 are docked with the plasma membrane, with 50–100 granules in a pool of immediate release, and other $\sim$1500 are located close to cell surface [70,30]. Granule exocytosis requires the fusion of granule membrane with plasma membrane and the formation of a pore that connects granule lumen to extracellular space. Incomplete fusion and kiss-and-run exocytosis may also occur.

As found by early observations *in vitro* and *in vivo*, stimulation by a rapid and large increase in the extracellular glucose concentration induces a biphasic time course of the insulin secretion rate (ISR) with a 5–10 min peak, the first phase, followed by a more prolonged second phase. These features were modeled by the early mathematical models [37,16]. Recent experimental data from mouse and rat β-cells showed that only 1–2 granules/min per β-cell are released at a glucose concentration around 3 mM, and 20–30 granules/min per cell are released at the peak of the first-phase insulin secretion after a step increase in glucose, with a total secretion of about 680 granules in 50 min (for instance, see [79]).

In a first pathway of stimulus-secretion coupling (triggering pathway), the glucose stimulus increases the ATP/ADP ratio, which induces closing of the K_{ATP} channels and depolarization of cell membrane. The resulting Ca^{2+} influx through the voltage-sensitive Ca^{2+} channels raises the cytosolic free calcium concentration, $[Ca^{2+}]^c$, so promoting the exocytosis of insulin granules. Still not completely characterized are the mediators of the amplifying pathway, that augments the efficacy of Ca^{2+} in stimulating the insulin secretion [38,30,39].

2.1.1. Mathematical models

Shibasaki et al. [74] used a model based on a three-dimensional random walk process to simulate the movement of insulin granules in an idealized β-cell. The introduction of a bias, that represented the recruitment of granules to plasma membrane, produced the second-phase response. The first phase was simulated by assuming that the randomly distributed granules had an increased density near the plasma membrane, so representing a pool of immediately releasable granules. Simulation results were in agreement with the observation that cAMP promotes exocytosis by both increasing the size and accelerating the refilling of the pool of immediate release.

The model proposed in [11] defines a pool, I, of free proinsulin and a pool, V, of free granule membrane material, not yet enclosing proinsulin. Moreover, four pools of insulin granules were considered: the reserve pool (R), the docked granules (D), the immediately releasable granules (D_{IR}), and the granules fused with cell membrane (F). Model equations are as follows:

$$\frac{dI}{dt} = -kI(t)V(t) - \alpha_I I(t) + b_I, \tag{1}$$

$$\frac{dV}{dt} = -kI(t)V(t) - \alpha_V V(t) + b_V + \sigma F(t-\tau_V), \tag{2}$$

$$\frac{dR}{dt} = kI(t)V(t) - \gamma(t)R(t), \tag{3}$$

$$\frac{dD}{dt} = \gamma(t)R(t) - k_1^+[C_T - D_{IR}(t)]D(t) + k_{-1}^- D_{IR}(t), \tag{4}$$

$$\frac{dD_{IR}}{dt} = k_1^+[C_T - D_{IR}(t)]D(t) - k_{-1}^- D_{IR}(t) - \rho(t)D_{IR}(t), \tag{5}$$

$$\frac{dF}{dt} = \rho(t)D_{IR}(t) - \sigma F(t). \tag{6}$$

In (1) and (2), k is an aggregation rate constant, α_I, α_V are degradation rate constants, and b_I, b_V denote, respectively, the rate of proinsulin biosynthesis and the production rate of granule membranes. The last term in the right-hand side of (2) accounts for the contribution to granule membrane formation of the recycling of membrane material, with σ the rate constant of the fusion process and τ_V the time interval required for recycling. The variable γ in (3) represents the processes by which granules are irreversibly translocated from trans-Golgi network to plasma membrane, and it is dependent on the glucose concentration, G, according to (7). The pool D_{IR} is formed through the binding of docked granules to L-type Ca^{2+} channels, with C_T denoting the pool of total Ca^{2+} channels and k_1^+, k_1^- the rate constants of association and, respectively, dissociation. The factors that promote granule fusion are represented by ρ, and $\sigma F(t)$ in (6) is the number of granules releasing insulin in the unit time at time t in a single β-cell.