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First phase release coefficient of insulin in subjects with normal glucose tolerance on glucose infusion analyzed by computer simulation

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Abstract

We report here a mathematical model using computer simulation to solve the phase fractionation coefficient (f) of instantaneous insulin release on glucose infusion. By extensive model testing with the cited parameters obtained from the literature, the values of the factor f were shown to lie in range of 0.93 ± 0.02 (mean $\pm$ 2S.D., $n = 15$), indicating that the high pulsatile bolus of glucose by i.v. infusion may trigger acute insulin release (AIR) corresponding to a fraction of more than 90% of the stored insulin release in the first phase from the secretory granules of pancreatic β cells. In addition, the value of the factor f was shown to be independent of both the glucose infusion method and the non-insulin-dependent uptake of glucose.

Keywords: Phase fractionation coefficient; Insulin release; Glucose infusion

1. Introduction

Early in 1969, Porte and Pupo had speculated a two-pool system concept to describe the insulin response to glucose in man (Porte and Pupo, 1969). However, the response pattern is highly nonlinear. In response to intravenous (i.v.) glucose, insulin is released in a biphasic pattern (Porte and Pupo, 1969; Nesher and Cerasi, 2002). The first phase (acute) insulin response to glucose begins within 1 min after an i.v. glucose bolus, peaks between 3 and 5 min, and lasts for up to 10 min. The second phase insulin response to glucose begins just after the glucose bolus but is not evident until 10 min later and lasts as long as the hyperglycemia persists (Cerasi, 1992; Elrick et al., 1964; Darren et al., 2006).

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Both oral and intravenous glucose tolerance tests are widely used to evaluate glucose metabolism in man. Intravenous methods permit the calculation of a specific rate constant for glucose utilization from a relationship of blood glucose and the time course of tracing the experimentation, whereas oral glucose tolerance testing (OGTT) is not a precise or reproducible method, because it could be handicapped by the variable of individual intestinal absorption. Elrick et al. (1964) had reported that glucose administered orally evokes a significantly greater insulin response than does glucose administered intravenously.

The acute insulin response (AIR) following intravenous glucose stimulation, which has been defined as the mean of the increments in serum immuno-reactive insulin (IRI) above baseline at 3–5 min, appears to be an important determinant of carbohydrate tolerance (Lerner and Porte, 1971). Thus, while the OGTT is a good measure of overall glucose tolerance, the intravenous glucose tolerance test (IVGTT) is preferable for evaluating glucose-regulated insulin secretion and β cell function (Elrick et al., 1964).

Bergman and colleagues (Bergman et al., 1985; Pacini et al., 1982) developed the minimal model approach, based on analysis of a frequently sampled i.v. glucose tolerance test (FSIGT). In vivo glucose tolerance is determined by both insulin-dependent and non-insulin-dependent processes. Two important metabolic parameters related to these two processes are estimated by the minimal model-insulin sensitivity (S_I), which characterizes insulin action on glucose kinetics, and glucose effectiveness (S_G), which characterizes non-insulin-dependent glucose kinetics at basal insulin (Ni et al., 1997). However existing approaches to FSIGT analysis are based on data of endogenous insulin secretion so that it could be applicable to a wide variety of clinical problems. While its method of resolution has long been handicapped by lacking a relevantly proper experimental approach, to our knowledge, we are the first to present such a mathematical model using computer simulation to solve for the phase fractionation factor of the stored insulin release.

2. The Model Derivation

The model describing the phase fractionation of the insulin release initiated either by a single glucose bolus or a hyperglycemic clamp test is exhibited in Appendix A from which some major equations that were used in the computer simulation are summarized in Table 1.

3. Materials and Methods

3.1. Subjects

Twelve volunteers without any family history of diabetes were involved in experimentation after given informed consent.

Table 1
A summary of the major equations relevant to the glucose–insulin interaction

Use of equation	Equation	Remark
Glucose utilization	$\gamma = R_{max}(C_{inf} - C_{pl})/K_s + (C_{inf} - C_{pl})$	
Phase 1: net insulin release	$\left(\frac{dN}{dt}\right)_{net,(1)} = \left(\frac{dN_r}{dC}\right)\left[\left(\frac{dC}{dt}\right)_{inf}\Big\vert^{t_{inf}}\right] - \frac{(dN_c/dC)R_{max}(C_{inf}-C_{pl})}{K_s+(C_{inf}-C_{pl})}$	Only the stored insulin is concerned, normally this takes 10 min
Phase 2: net insulin release	$\left(\frac{dN}{dt}\right)_{net,(2)} = \left[\frac{1-f}{f}\right]\left\{\left(\frac{dN_r}{dC}\right)\left[\left(\frac{dC}{dt}\right)_{inf}\Big\vert^{t_{inf}}\right]\right\} + \left(\frac{dN_s}{dC}\right)\left\{\frac{R_{max}(C_{inf,10}-C_{pl})}{K_s+(C_{inf,10}-C_{pl})}\right\} - \left(\frac{dN_c}{dC}\right)\left\{\frac{R_{max}(C_{inf,10}-C_{pl})}{K_s+(C_{inf,10}-C_{pl})}\right\}$	Involving both the insulin from the residual stored and the de novo synthesis. For normal subjects, phase 2 lasts for 60 min, however it only becomes significant at 10 min post a single glucose bolus.
Overall: net insulin release	$\left(\frac{dN}{dt}\right)_{net,overall} = \left(\frac{dN_r}{dC}\right)\left[\left(\frac{dC}{dt}\right)_{inf}\Big\vert^{t_{inf}}\right] - \frac{(dN_c/dC)R_{max}(C_{inf}-C_{pl})}{K_s+(C_{inf}-C_{pl})]} + \left[\frac{1-f}{f}\right]\left\{\left(\frac{dN_r}{dC}\right)\left[\left(\frac{dC}{dt}\right)_{inf}\Big\vert^{t_{inf}}\right]\right\} + \left(\frac{dN_s}{dC}\right)\left\{\frac{R_{max}(C_{inf,10}-C_{pl})}{K_s+(C_{inf,10}-C_{pl})]}\right\} - \left(\frac{dN_c}{dC}\right)\left\{\frac{R_{max}(C_{inf,10}-C_{pl})}{K_s+(C_{inf,10}-C_{pl})]}\right\}$	By a single glucose bolus; named herein; the model of insulin response to glucose bolus (MIRGLuB)
Overall: net insulin release in hyperglycemic clamp	$\left(\frac{dN}{dt}\right)' = \left(\frac{dN_r}{dC}\right)\left[\left(\frac{dC}{dt}\right)_{inf}\Big\vert^{t_{inf}}\right] - \left(\frac{dN_c}{dC}\right)\left\{\frac{R_{max}(C_{inf}-C_{pl})}{K_s+(C_{inf}-C_{pl})}\right\} + \left[\frac{1-f}{f}\right]\left\{\left(\frac{dN_r}{dC}\right)\left[\left(\frac{dC}{dt}\right)_{inf}\Big\vert^{t_{inf}}\right]\right\} + \left(\frac{dN_s}{dC}\right)\left\{C_{inf} - \left\{\frac{R_{max}(C_{inf}-C_{pl})}{K_s+(C_{inf}-C_{pl})}\right\}\right\} - \left(\frac{dN_c}{dC}\right)\left\{\frac{R_{max}(C_{inf}-C_{pl})}{K_s+(C_{inf}-C_{pl})}\right\}$	By hyperglycemic clamp test at a certain glucose concentration C_{inf}; the model of insulin response to hyperglycemic clamp test (MIRHyCT)