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Estimation of insulin secretion, glucose uptake by tissues, and liver handling of glucose using a mathematical model of glucose-insulin homeostasis in lean and obese mice

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Abstract

Destruction of the insulin-producing β-cells is the key determinant of diabetes mellitus regardless of their types. Due to their anatomical location within the islets of Langerhans scattered throughout the pancreas, it is difficult to monitor β-cell function and mass clinically. To this end, we propose to use a mathematical model of glucose-insulin homeostasis to estimate insulin secretion, glucose uptake by tissues, and hepatic handling of glucose. We applied the mathematical model by Lombarte et al. (2013) to compare various rate constants representing glucose-insulin homeostasis between lean (11% fat)- and high fat diet (HFD; 45% fat)-fed mice. Mice fed HFD (n = 12) for 3 months showed significantly higher body

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weights (49.97 ± 0.52 g vs. 29.86 ± 0.46 g), fasting blood glucose levels (213.08 ± 10.35 mg/dl vs. 121.91 ± 2.26 mg/dl), and glucose intolerance compared to mice fed lean diet (n = 12). Mice were injected with 1 g/kg glucose intraperitoneally and blood glucose levels were measured at various intervals for 120 min. We performed simulation using Arena^{TM} software based on the mathematical model and estimated the rate constants (9 parameters) for various terms in the differential equations using OptQuest^{TM}. The simulated data fit accurately to the observed data for both lean and obese mice, validating the use of the mathematical model in mice at different stages of diabetes progression. Among 9 parameters, 5 parameters including basal insulin, k_2 (rate constant for insulin-dependent glucose uptake to tissues), k_3 (rate constant for insulin-independent glucose uptake to tissues), k_4 (rate constant for liver glucose transfer), and I_{pi} (rate constant for insulin concentration where liver switches from glucose release to uptake) were significantly different between lean- and HFD-fed mice. Basal blood insulin levels, k_3, and I_{pi} were significantly elevated but k_2 and k_4 were reduced in mice fed a HFD compared to those fed a lean diet. Non-invasive assessment of the key components of glucose-insulin homeostasis including insulin secretion, glucose uptake by tissues, and hepatic handling of glucose may be helpful for individualized drug therapy and designing a customized control algorithm for the artificial pancreas.

Keywords: Mathematical bioscience

1. Introduction

Diabetes Mellitus is a widespread disease currently affecting 29.1 million Americans, or 9.3% of the total population (American Diabetes Association 2012 statistics). Furthermore, additional 86 million Americans are considered pre-diabetic, implying an alarming growth rate of the diabetes epidemic in the future. Two major forms of diabetes are type 1 and type 2 diabetes mellitus (T1DM and T2DM). T1DM is a chronic, progressive autoimmune disease caused by selective destruction of insulin-producing β-cells within the pancreatic islets of Langerhans [1]. Insulin delivered through an insulin pump or daily injections is essential to sustain life for these patients. The onset of T1DM occurs at an early age (young children and teens), hence, previously called juvenile diabetes. Even though T1DM comprises only 5–10% of diabetic patients, incidence of T1DM is rising at 3% per year [2] and the burden of the disease affecting children at young ages extending throughout their lives is enormous. Despite careful monitoring, a subset of patients with complicated T1DM are at high risk of life-threatening hypoglycemia episodes. Emerging new treatments for these patients include β-cell replacement therapy and closed-loop artificial pancreas device (APD) systems. The APD systems are externally worn medical devices under development, which consists of 3 components including continuous glucose monitoring sensor, insulin pump, and

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