The graded glucose infusion (GGI) procedure has been used to evaluate β cell function independently of insulin sensitivity. Quantification of insulin secretion rate (ISR) using the GGI provides insight into the trajectories of β cell dysfunction in the development of diabetes and could be used to directly evaluate the effects of therapeutic agents on β cell function. ISR was determined by deconvolution of serum C-peptide concentrations measured during a 5 stage GGI (glucose infusion rates of 2, 4, 8, 16, and 32mg/kg/min for 40 mins each) in three groups of cynomolgus monkeys: 6 normal (6.0 ± 0.2yrs), 7.6 ± 0.7kg, fasting glucose: 60 ± 4mg/dL), 14 prediabetic (15.0 ± 0.8yrs, 9.0 ± 0.9kg, fasting glucose: 80 ± 4mg/dL); and 4 untreated newly diabetic (16.0 ± 1.2yrs, 9.0 ± 1.8kg, fasting glucose: 169 ± 22mg/dL). After correction for circulating plasma glucose concentrations, group mean ISRs were compared by one-way ANOVA with Tukey’s post hoc comparisons. A significant mean difference in ISR was found between the groups (F=6.18, p=0.001). ISR was significantly lower in the diabetic group compared to the normal (28.0%, p=0.01) and prediabetic groups (26.2%, p=0.05). The plasma glucose-corrected ISR did not differ significantly between the normal and prediabetic groups. We conclude that the GGI procedure for calculation of the glucose-stimulated insulin secretory rates clearly identified the differences in β cell secretory responses in normal, prediabetic, and diabetic cynomolgus monkeys. These results clearly demonstrated the efficacy of agents targeting functional improvements in β cell function.

Introduction

β cell functional failure is an important defect leading to overt manifestation of type 2 diabetes and therefore represents a key pharmacological target. The application of robust methodologies to quantify β cell responsiveness in a highly clinically-relevant animal model is essential for future therapeutic development efforts. Herein, we describe the application of the graded glucose infusion procedure with C-peptide deconvolution to quantify the insulin secretion rate in metabolically healthy, pre-diabetic, and diabetic cynomolgus macaques.

Abstract

Methods

Insulin Secretion Rate (ISR)

Given its negligible hepatic clearance, C-peptide concentration in the peripheral vasculature is an indirect indicator of pre-hepatic insulin secretion. Under non-steady state conditions, C-peptide kinetics are non-linear and subject to convolution. C-peptide secretion (and hence, pre-hepatic insulin secretion) patterns can be reassembled using deconvolution procedures. We used the Regularization Method of deconvolution as implemented in the software program ISEC (Hovorka, 1996) to determine the insulin secretion rate (ISR).

Results

Comparison of insulin secretion rate among groups: ISR was significantly lower in diabetic monkeys than in the prediabetic (p<0.05) and normal (p<0.01) groups after adjusting for plasma glucose. After adjusting for differences in blood glucose concentrations, ISR did not differ between the normal and prediabetic monkeys. These results clearly demonstrated a compromised pancreatic β-cell function in the diabetic animals.

Conclusion

The graded glucose infusion combined with C-peptide deconvolution to derive the insulin secretion rate documented different glucose-stimulated β cell responses in normal, prediabetic, and diabetic cynomolgus macaques. This method provides a useful approach for preclinical assessment of the efficacy of novel pharmaceutical agents targeting improvements in β cell function in this clinically-relevant nonhuman primate model.

Fig. 1 – Graded glucose infusion (GGI) procedure

Fig. 2 – Descriptive data on metabolically normal, pre-diabetic, and diabetic monkeys, “p<0.05 vs. normal Sample descriptive data: Diabetic and prediabetic monkeys were significantly older than their healthy counterparts. Body weight was significantly higher among the prediabetic and diabetic groups relative to the metabolically normal group (after adjusting for sex). Fasting blood glucose concentrations were higher in the diabetic monkeys relative to the prediabetic and normal monkeys.

Fig. 3 – Mean (±SE) for glucose, insulin, and C-peptide concentrations at all time points during the GGI Metabolic response to GGI: Predictably, plasma glucose values rose highest in the absence of a robust insulin secretory response in the diabetic group, while insulin responses were greatest in the prediabetic monkeys.

Fig. 4 – Insulin secretion rate (ISR) by C-peptide deconvolution

Fig. 5 – Insulin secretion rate (ISR) plotted against blood glucose concentrations

Quantification of glucose-stimulated insulin secretion rate in normal, pre-diabetic, and diabetic cynomolgus monkeys (Macaca fascicularis) using a graded glucose infusion (GGI)

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