A well-established approach for the estimation of insulin secretion in vivo is based on the measurement of plasma C-peptide. C-peptide is secreted by pancreatic β-cells in equimolar amounts with insulin, but unlike insulin, C-peptide is not extracted by the liver and has a constant peripheral clearance. Thus, the systemic (venous) appearance of C-peptide equals the pancreatic release of insulin. The C-peptide systemic appearance can be calculated by deconvolution from the plasma C-peptide concentrations and a kinetic model of C-peptide distribution (1). This method has been used to evaluate 24-h profiles of insulin secretion (2) and the β-cell dose-response curve (3).

We developed a model for assessing the 24-h profile of insulin secretion and its control by glucose, simultaneously. To date, the model has been tested in lean and obese non-diabetic subjects.

RESEARCH DESIGN AND METHODS

A total of 20 obese subjects (BMI 50 ± 2 kg/m²) and 7 nonobese (BMI 27 ± 1 kg/m²) age- and sex-matched control subjects spent 24 h in a calorimetric chamber under standardized conditions of diet and physical activity. Four meals were administered for a total caloric intake of 30 kcal per kg of lean body mass (20% breakfast, 40% lunch, 10% afternoon snack, and 30% dinner). The diet consisted of 17% protein, 35% fat, and 48% carbohydrate. In each subject, central venous blood (for measurement of glucose, insulin, and C-peptide) was sampled hourly through an indwelling catheter, which was derived externally via an airtight port of the chamber. Insulin secretion rates (ISR) were reconstructed from C-peptide levels by deconvolution and related to concomitant glucose concentrations, a submodel for C-peptide kinetics, and a submodel for the pancreatic release of insulin. The C-peptide systemic appearance can be calculated by deconvolution from the plasma C-peptide concentrations and a kinetic model of C-peptide distribution (1). This method has been used to evaluate 24-h profiles of insulin secretion (2) and the β-cell dose-response curve (3).

RESULTS

Insulin secretion and its components are shown in Fig. 2. The four secretory peaks corresponding to the meals are clearly visible. Approximately 80% of insulin secretion could be related to glucose levels in a functional form (the first two terms of the insulin secretion submodel), whereas the remainder was accounted for by the residual term S(t). The term p3G(t) was generally small. The residual term S(t) was variable among subjects. The range of the standard deviation of S(t) was 41–319 pmol/min. The time course of S(t) indicates that insulin secretion was lower during the night compared with during the day, even after accounting for the lower glucose levels, suggesting that insulin secretion may follow an inherent circadian pattern. The presence of secondary peaks in S(t), which bear some relation to the main peaks of insulin secretion, may indicate the existence of secretory features not included in the model. Diurnal ISR was 75 ± 8 vs. 36 ± 3 U (P = 0.007 obese subjects vs. control subjects), whereas nocturnal ISR was 11 ± 1 vs. 4 ± 1 U (P = 0.002). The diurnal-to-nocturnal ISR ratio is 6.8 ± 0.3 vs. 9.0 ± 1.0.

The average β-cell dose-response functions are shown in Fig. 3 for the obese subjects and the control subjects. The β-cell sensitivity index represented by insulin secretion at 8 mmol/l glucose concentration was correlated with the parameter representing the sensitivity of the β-cell to the glucose rate of change, p3 (R = 0.84, P < 0.0001). This indicates that both of these β-cell sensitivity indexes reflect pancreatic function, despite the fact that the insulin secretion component was small, due to the glucose rate of change. Clearly, the dose-response curve for the obese subjects is shifted to the left and upwards of that for the control subjects, but the secretory response to the highest observed glucose level (10 mmol/l) was similar between the two groups. The model indicated that in the obese group, whereas ISR at basal glucose (4 mmol/l) was strongly enhanced (317 ± 38 vs. 91 ± 32 pmol/min, P = 0.002), β-cell glucose sensitivity was actually depressed (160 ± 40 vs. 1,393 ± 495, P = 0.0002). In the entire database, insulin secretion at 4 mmol/l glucose (i.e., basal insulin secretion) was directly related to the mean 24-h plasma concentration of free fatty acids, suggesting a role for this substrate in the tonic maintenance of basal insulin production.


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ISR, insulin secretion rates.

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A Model for Assessing Insulin Secretion and Its Control Under Free-Living Conditions

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CONCLUSIONS

This model can reconstruct 24-h profiles of insulin secretion under free-living conditions and relate them to glucose and nonglucose secretagogues in a functional manner. The performance of the model and some preliminary defining characteristics of the secretory function have been determined in lean and morbidly obese subjects. The insulin hypersecretion of these patients could be specified as increasing overall insulin output and greatly enhancing basal (i.e., at low glucose) ISR, but reducing sensitivity of ISR to glucose changes. Application of this model to subjects with reduced glucose tolerance or overt diabetes should provide both qualitative and quantitative information on the role of β-cell dysfunction in diabetes.

REFERENCES