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Dynamics of insulin secretion in obesity and diabetes

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Insulin resistance and compensatory hyperinsulinemia are commonly present in obesity. The biochemical mechanisms responsible for the maintenance of basal hypersecretion of insulin are reviewed in this article. Under basal, fasting and fed conditions the hyperinsulinemia of obesity largely depends on increased insulin secretion, without any alteration of the temporal secretion. This suggests that the functioning beta cell mass is enhanced, but normal regulatory mechanisms are maintained. A number of alterations in β-cell function are present in conditions of impaired glucose tolerance which precede the onset of overt diabetes.
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Introduction

The vast majority of obese individuals are insulin resistant. When insulin resistance is present the maintenance of normal glucose tolerance is dependent on the ability of the beta cell to increase insulin secretion in order to compensate for the reductions in insulin action. This compensation involves mechanisms that increase the sensitivity of the beta cell to a glucose stimulus resulting in a shift to the left in the dose–response curve relating glucose and insulin secretion.

In order to explore the biochemical mechanisms responsible for the maintenance of hypersecretion of insulin at low glucose, we examined changes in high and low K_m glucose phosphorylating activity in pancreatic islet extracts from the prediabetic Zucker diabetic fatty (ZDF) rat between 5–6 weeks and 12 weeks of age (after the onset of diabetes).[1]

Comparisons were made between the activity observed in the ZDF rat and that seen in the ZDF lean control (ZLC) rat and the obese nondiabetic Zucker fatty (ZF) rat. At 5–6 weeks of age, insulin resistant ZDF and ZF rats were hyperinsulinemic, compared with the ZLC rat, but had normal plasma glucose levels. Kinetic parameters (V_{max} and K_m for glucose) of hexokinase (HK) and K_m of glucokinase (GCK) did not differ between groups. Islet GCK activity for ZDF and ZF rats was 1.7 fold greater than in ZLC rats ($P < 0.02$ and $P < 0.001$, respectively). By 12 weeks of age, hypersecretion of insulin at 5.0 mmol/l glucose was observed in perifused islets from both obese groups relative to the ZLC rat. Islets from ZDF rats failed to increase insulin secretion in response to increased glucose concentration. Group differences in the kinetic parameters for GCK or in the K_m values for HK were not significant. Islet HK activity for ZDF and ZF rats was 1.9-fold ($P < 0.05$) and 1.7-fold ($P < 0.05$) greater, respectively, than for ZLC rats. Compared with the 5–6-week-old animals, HK activity increased 3.1-fold ($P < 0.001$), 2.5-fold ($P < 0.002$), and 2.0-fold ($P < 0.05$) for ZDF, ZF and ZLC rats, respectively. Differences in GCK activity between 5–6- and 12-week-old rats were not significant for any of the groups. These results have allowed us to conclude that: (1) increased islet glucose phosphorylating activity is present in insulin resistant and hyperinsulinemic ZF and ZDF rats, relative to the ZLC rat; (2) at 12 weeks of age, hyperinsulinemic ZDF and ZF rats demonstrated significant increases in HK activity, compared with lean controls; and (3) deficiency in GCK activity does not explain failure of diabetic ZDF islets to respond to glucose, since differences between diabetic ZDF and nondiabetic ZF rats were not statistically significant. Increases in pancreatic islet phosphorylating activity seem to be important in maintaining basal hyperinsulinemia in insulin-resistant animals, but do not appear to play a role in the progression to glucose intolerance and diabetes.

Changes in insulin secretion *in vivo* in humans with insulin resistance

The secretion and hepatic extraction of insulin were compared in 14 normal volunteers and 15 obese

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subjects[2] using a previously validated mathematical model of insulin secretion and rate constants for C-peptide derived from analysis of individual decay curves after intravenous bolus injections of bio-synthetic human C-peptide.[3] Insulin secretion rates were substantially higher than normal in the obese subjects after an overnight fast (86.7 ± 7.1 *vs* 50.9 ± 4.8 pmol/m^2 per min, $P < 0.001$, mean $\pm$ s.e.m.), over a 24 h period on a mixed diet (279.6 ± 24.2 *vs* 145.8 ± 8.8 pmol/m^2 per 24 h $P < 0.001$), and during a hyperglycemic intravenous glucose infusion (102.2 ± 10.8 *vs* 57.2 ± 2.8 pmol/m^2 per 180 min, $P < 0.001$). Linear regression analysis revealed a highly significant relationship between insulin secretion and body mass index.

Basal hepatic insulin extraction was not significantly different in the normal and obese subjects (53.1 ± 3.8 *vs* 51.6 ± 4.0%). In the normal subjects, fasting insulin did not correlate with basal hepatic insulin extraction, but a significant negative correlation between fasting insulin and hepatic insulin extraction was seen in obesity ($r = -0.63$, $P < 0.02$). This finding reflected a higher extraction in the six obese subjects with fasting insulin levels within the range of the normal subjects than in the nine subjects with elevated fasting insulin concentrations (61 ± 3 *vs* 45 ± 6%, $P < 0.05$).

During the hyperglycemic clamp, the insulin secretion rate increased to an average maximum of 6.2-fold over baseline in the normal subjects and 5.8-fold in the obese subjects. Over the same time, the peripheral insulin concentration increased 14.1-fold over baseline in the normals and 16.6-fold over baseline in the obese, indicating a reduction in the clearance of endogenously secreted insulin. Although the fall in insulin clearance tended to be greater in the obese subjects, the differences between the two groups were not statistically significant.

Thus, under basal, fasting conditions and during ingestion of a mixed diet, the hyperinsulinemia of obesity results predominantly from increased insulin secretion. In patients with more marked basal hyperinsulinemia and during intense stimulation of insulin secretion, a reduction in insulin clearance may contribute to the greater increase in peripheral insulin concentrations that are characteristic of the obese state. The pattern of endogenous insulin secretion of a 24 h period, which included three mixed meals, was evaluated in 14 normal volunteers and 15 obese subjects.[4]

Insulin secretory rates were calculated from plasma C-peptide levels using individually derived C-peptide kinetic parameters and a validated open two-compartment model of peripheral C-peptide kinetics. Insulin secretion rates were consistently elevated in the obese subjects under basal conditions (11.6 ± 1.2 *vs* 5.4 ± 0.5 nmol/h) and in the 4 h after breakfast (139 ± 15 *vs* 63 ± 5 nmol/4 h, $P < 0.001$), lunch (152 ± 16 *vs* 67 ± 5 nmol/4 h, $P < 0.001$), and dinner (145 ± 18 *vs* 65 ± 6 nmol/4 h, $P < 0.001$).

In the normal subjects, basal insulin secretion represented 50 ± 2.1% of total 24 h insulin production, insulin secretion returned to baseline between meals, and equal quantities of insulin were secreted in the 4 h after breakfast, lunch and dinner, despite the fact that subjects consumed half the number of calories at breakfast compared with lunch and dinner. Overall glucose responses were also similar after the three meals.

In contrast, the pattern of insulin secretion in obese subjects was largely normal, albeit set at a higher level. However, the insulin secretion rate after meals did not return to baseline, and the secretion rate immediately before lunch (350.5 ± 81.9 pmol/min) and dinner (373.6 ± 64.8 pmol/min) was considerably higher than the secretion rate immediately before breakfast (175.5 ± 18.5 pmol/min). In these overweight subjects, the glucose response after lunch was lower than after dinner.

Analysis of individual 24 h insulin secretory profiles in the normal subjects revealed that insulin secretion was pulsatile. On average 11.1 ± 0.5 pulses were produced in each 24 h period. The most prevalent temporal distribution of postmeal secretory pulses was two pulses after breakfast and three pulses after both lunch and dinner. Insulin secretion was also pulsatile during the period without meal stimuli: 3.9 ± 0.3 pulses occurred during the period of overnight sampling and in the 3 h period before ingestion of the breakfast meal. In the obese subjects, the number of timing of secretory pulses was similar to those of normal volunteers, although the amplitude of the pulses was significantly greater. In both groups of subjects, > 80% of insulin pulses were concomitant with a pulse in glucose concentration in the postmeal period. The concomitancy rate was significantly lower in the interval without the meal stimuli, averaging 47% in both groups.

Thus in obesity, although hypersecretion of insulin can be documented, the temporal pattern of secretion is largely unaltered, which suggests that the functioning β-cell mass is enhanced, but normal regulatory mechanisms influencing secretion are still operative.

In order to determine if impaired glucose tolerance is consistently associated with changes in insulin secretion,[5] studies were performed in subjects with no known family history of diabetes normoglycemic subjects who have first-degree relatives with non-insulin-dependent diabetes mellitus (NIDDM), and subjects with nondiagnostic oral glucose tolerance tests (NDX) or impaired glucose tolerance (IGT). Insulin sensitivity index (S_i) was similar in all four groups. However, a number of defects in insulin secretion were seen in the NDX and IGT groups, including reduced first-phase insulin secretory responses to intravenous glucose in relation to the degree of insulin resistance, and reduced normalized spectral power of insulin secretion during oscillatory glucose infusion. The latter finding demonstrates a decreased ability of the β-cell to detect and respond to

the successive increases and decreases in glucose and therefore to be entrained by the exogenous glucose infusion. The ability of a low-dose glucose infusion to prime the insulin secretory response to a subsequent glucose stimulus was normal in subjects with IGT but reduced or absent in subjects with overt NIDDM. These studies demonstrate that a number of alterations in β-cell function are detectable in nondiabetic first-degree relatives of subjects with NIDDM with mild elevations in the 2 h postchallenge glucose level, and these abnormalities antedate the onset of overt hyperglycemia and clinical diabetes.

Normal subjects demonstrate the presence of ultradian oscillations (period 80–150 min) in insulin secretion rate (ISR) tightly coupled to glucose oscillations of similar period. These oscillations appear to be a function of the feedback loop linking glucose and insulin. We determined whether the control by glucose of the ultradian oscillations in insulin secretion is altered in impaired glucose tolerance IGT and in non-insulin-dependent diabetes mellitus (NIDDM).[6] Patients with NIDDM ($n=7$), IBT ($n=4$), and matched non-diabetic controls ($n=5$) were studied under three separate protocols that involved administration of glucose at either a constant rate of 6 mg/kg per min for 28 h or in one of two oscillatory patterns at the same overall mean rate. The amplitude of the oscillations was 33% above and below the mean infusion rate, and their respective periods were 144 min (slow oscillatory infusion) or 96 min (rapid oscillatory infusion). Insulin, C-peptide and glucose were sampled at 10 min intervals during the last 24 h of each study. ISRs were calculated by deconvolution of C-peptide levels. Analysis of the data showed that (a) the tight temporal coupling between glucose and ISR in the non-diabetic controls was impaired in the IGT and NIDDM groups as demonstrated by pulse analysis, cross-correlation analysis, and spectral analysis; (b) the absolute amplitude of the ISR pulses progressively declined with the transition from obesity to IGT to NIDDM; and (c) the absolute amplitude of the ISR oscillations failed to increase appropriately with increasing absolute amplitude of glucose oscillation in the IGT and NIDDM subjects compared with the control group. In conclusion, the present study demonstrates that important dynamic properties of the feedback loop linking insulin secretion and glucose are disrupted not only in established NIDDM but also in conditions where glucose tolerance is only minimally impaired. Further studies are needed to determine how early in the course of beta-cell dysfunction this lack of control by glucose of the ultradian oscillations in insulin secretion occurs and to define more precisely if this phenomenon plays a pathogenetic role in the onset of hyperglycemia in genetically susceptible individuals.[6]

To determine whether non-insulin-dependent diabetes is associated with specific alterations in the pattern of insulin secretion, we studied 16 patients with untreated diabetes and 14 matched controls.[7]

The rates of insulin secretion were calculated from measurements of peripheral C-peptide in blood samples taken at 15–20 minute intervals during a 24 h period in which the subjects ate three mixed meals.

Incremental responses of insulin secretion to meals were significantly lower in the diabetic patients ($P < 0.005$), and the increases and decreases in insulin secretion after meals were more sluggish. These disruptions in secretory response were more marked after dinner than after breakfast, and a clear secretory response to dinner often could not be identified.

Both the control and diabetic subjects secreted insulin in a series of discrete pulses. In the controls, a total of seven to eight pulses were identified in the period from 9 a.m. to 11 p.m., including the three postmeal periods (an average frequency of one pulse per 105–120 min), and two to four pulses were identified in the remaining 10 h. The number of pulses in the patients and controls did not differ significantly. However, in the patients, the pulses after meals had a smaller amplitude ($P < 0.03$) and were less frequently concomitant with a glucose pulse (54.7 ± 4.9 *vs* $82.2 \pm P < 0.001$). Pulses also appeared less regularly in the patients. During glucose clamping to produce hyperglycemia (glucose level, 16.7 mmol/l (300 mg/dl), the diabetic subjects secreted, on average, 70% less insulin than matched controls ($P < 0.001$).

These data suggests that profound alterations in the amount and temporal organization of stimulated insulin secretion may be important in the pathophysiology of beta-cell dysfunction in diabetes.[7]

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