Different Mechanisms for Impaired Fasting Glucose and Impaired Postprandial Glucose Tolerance in Humans

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OBJECTIVE — To compare the pathophysiology of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) in a more comprehensive and standardized fashion than has hitherto been done.

RESEARCH DESIGN AND METHODS — We studied 21 individuals with isolated IFG (IFG/normal glucose tolerance [NGT]), 61 individuals with isolated IGT (normal fasting glucose [NFG]/IGT), and 240 healthy control subjects (NFG/NGT) by hyperglycemic clamps to determine first- and second-phase insulin release and insulin sensitivity. Homeostasis model assessment (HOMA) indexes of β-cell function (HOMA-%B) and insulin resistance (HOMA-IR) were calculated from fasting plasma insulin and glucose concentrations.

RESULTS — Compared with NFG/NGT, IFG/NGT had similar fasting insulin concentrations despite hyperglycemia; therefore, HOMA-IR was increased ~30% ($P < 0.05$), but clamp-determined insulin sensitivity was normal ($P > 0.8$). HOMA-%B and first-phase insulin responses were reduced ~35% ($P < 0.002$) and ~30% ($P < 0.02$), respectively, but second-phase insulin responses were normal ($P > 0.5$). NFG/IGT had normal HOMA-IR but ~15% decreased clamp-determined insulin sensitivity ($P < 0.03$). Furthermore, HOMA-%B was normal but both first-phase ($P < 0.0003$) and second-phase ($P < 0.0001$) insulin responses were reduced ~30%. IFG/NGT differed from NFG/IGT by having ~40% lower HOMA-%B ($P < 0.012$) and ~50% greater second-phase insulin responses ($P < 0.005$).

CONCLUSIONS — Since first-phase insulin responses were similarly reduced in IFG/NGT and NFG/IGT, we conclude that IFG is due to impaired basal insulin secretion and preferential resistance of glucose production to suppression by insulin, as reflected by fasting hyperglycemia despite normal plasma insulin concentrations and increased HOMA-IR, whereas IGT mainly results from reduced second-phase insulin release and peripheral insulin resistance, as reflected by reduced clamp-determined insulin sensitivity.

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Abbreviations: DI, disposition index; EGP, endogenous glucose production; FSIVGTT, frequently sampled intravenous glucose tolerance test; HOMA, homeostasis model assessment; HOMA-%B, HOMA of β-cell function; HOMA-IR, HOMA of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ISI, insulin sensitivity index; NFG, normal fasting glucose; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Pre-diabetes is a category of glucose tolerance representing an intermediate stage between normal glucose tolerance (NGT) and diabetes. Within this category are two subcategories: impaired fasting glucose (IFG; defined as a fasting plasma glucose concentration of 100–125 mg/dl) and impaired glucose tolerance (IGT; defined as a 2-h oral glucose tolerance test [OGTT] plasma glucose concentration of 140–199 mg/dl) (1). Although both subcategories increase the risk for diabetes, current evidence suggests that they may have different pathophysiologies and different consequences. For example, most but not all studies indicate that IGT is a better predictor than IFG for all-cause mortality and/or cardiovascular morbidity/mortality (1). Furthermore, rates of endogenous glucose production (EGP) are proportional to fasting plasma glucose concentrations (2). Consequently, EGP would be expected to be greater in people with IFG than in those with isolated IGT.

The question thus arises whether IFG and IGT are fundamentally different conditions. The answer to this question could have important implications for their treatment and for interventions aimed at preventing the progression to diabetes.

A number of studies have assessed insulin secretion and sensitivity in individuals with isolated IFG and isolated IGT (3–10). Although virtually all indicate that the pathophysiologies of IFG and IGT may be different, these have not yielded consistent results regarding the differences in these conditions. In studies using homeostasis model assessment (HOMA), which has been used most commonly, insulin resistance (HOMA-IR) was at least equally if not more pronounced in IFG than IGT (3,5,6,8–10). In contrast, of the three studies (3,4,7) that assessed insulin sensitivity by more sophisticated measures, i.e., euglycemic clamps or frequently sampled intravenous glucose tolerance tests (FSIVGTTs), one (7) found IFG subjects not to be insulin resistant, whereas all three found IGT subjects to be insulin resistant. Furthermore, when subjects with isolated IFG and subjects with isolated IGT were compared with one an-

other, two studies (3,7) found better insulin sensitivity in the former group, while one study (4) found similar insulin sensitivity in both groups.

Studies using HOMA of β-cell function (HOMA-%B) have universally found lower β-cell function in individuals with isolated IFG than in those with isolated IGT (6–8). However, of the eight studies using OGTTs or FSIVGTTs (3–10), only four studies found impaired insulin secretion in the IFG group (3–5,10) and only five found impaired insulin secretion in the IGT group (3–5,9,10). When subjects with isolated IFG were compared with subjects with isolated IGT, two studies found better β-cell function in IFG (9,10), one study found worse β-cell function in IFG (3), and three studies found similar β-cell function in both groups (4,6,7). Thus, regarding both insulin secretion and insulin sensitivity, previous studies have not yielded consistent differences between IFG and IGT subjects.

There are several possible explanations for the inconsistent findings, including differences in study populations (i.e., Pima Indians versus a triethnic population versus mostly Caucasians) and methodological differences (HOMAs versus OGTTs versus FSIVGTTs for evaluation of β-cell function and HOMAs versus FSIVGTTs versus euglycemic clamps for evaluation of insulin sensitivity) and limitations. For example, in studies using OGTTs and FSIVGTTs for evaluation of β-cell function (3–10), plasma insulin responses were not adjusted for differences in glycemic stimuli and/or insulin sensitivity (11). Furthermore, insulin release is biphasic (12), and decreases in first- and second-phase insulin release are considered to be important for IGT (13). Whether decreases in both phases are also involved in IFG has, however, not been examined.

The present study was therefore undertaken to compare the pathophysiology of IFG and IGT in a more comprehensive and standardized manner than has hitherto been done. To this end, we used the hyperglycemic clamp technique to determine first- and second-phase insulin responses, as well as insulin sensitivity, in a large number of subjects with isolated IFG or isolated IGT and in healthy subjects with normal glucose homeostasis.

RESEARCH DESIGN AND METHODS

From 1986 to 2005, data were systematically collected from all individuals not known to have type 2 diabetes (n = 402); these subjects underwent a standard OGTT, as recommended by the American Diabetes Association, and a hyperglycemic clamp, as described below. All subjects gave informed written consent after the protocol had been approved by local institutional review boards. All participants were in good health and had normal physical examinations and routine laboratory tests. None of the subjects were taking any medications known to affect glucose metabolism.

Subjects were divided into different categories based on fasting plasma glucose concentrations (mean of two measurements at least 1 week apart) and 2-h plasma glucose concentrations during the standard 75-g OGTT. IFG was defined as fasting plasma glucose concentrations between ≥100 and <126 mg/dl and IGT as 2-h postchallenge plasma glucose concentrations between ≥140 and <200 mg/dl (1). The data of subjects who had fasting plasma glucose concentrations ≥126 mg/dl or 2-h postprandial glucose concentrations ≥200 mg/dl (n = 37) were eliminated for the purpose of the present study. This stratification resulted in four different groups of subjects: normal fasting glucose (NFG)/NGT (n = 240), IFG/NGT (n = 21), NFG/IGT (n = 61), and IFG/IGT (n = 43). Of these subjects, 197 were studied in the U.S., 83 in Brazil, 30 in the Netherlands, 21 in Italy, 20 in Greece, and 14 in Finland. The results of some of these subjects have been included in previous reports (14–17).

For 3 days before the study, all subjects were on a weight-maintaining diet containing at least 200 g carbohydrate and had abstained from alcohol and strenuous exercise. Subjects were admitted to a clinical research unit the evening before the experiments and given a standard dinner (10 kcal/kg: 50% carbohydrate, 35% fat, and 15% protein) between 6:30 and 7:00 P.M. Apart from water ad lib, subjects fasted thereafter until the experiments were completed. The following morning, a dorsal hand vein was cannulated in a retrograde fashion and kept in a thermoregulated Plexiglass box at 65°C for sampling arterialized venous blood (18). An antecubital vein was cannulated for infusion of 20% glucose. After a 30-min baseline period, plasma glucose concentrations were increased to 180 mg/dl (10 mmol/l) and subsequently maintained at this level for 180 min using the glucose clamp technique (19). During the experiments, blood samples for plasma insulin determinations were obtained at −30, −15, 0, 2.5, 5, 7.5, 10, 20, 40, 60, 80, 100, 120, 140, 160, and 180 min.

Analytical procedures

Plasma glucose concentrations were determined by a glucose analyzer (YSI Glucose Analyzer; Yellow Springs Instruments, Yellow Springs, OH, or Beckman Glucose Analyzer; Beckman Coulter, Fullerton, CA). Plasma insulin concentrations were determined using human insulin–specific radioimmunoassays (Pharmacia Insulin RIA; Kabi Pharmacia Diagnostics, Piscataway, NJ, or Linco Insulin RIA; Linco Research, St. Charles, MO).

Calculations

Basal insulin secretion was assessed by HOMA-%B, which was calculated as (fasting plasma insulin [pmol/l] × 3.33)/(fasting plasma glucose [mmol/l] − 3.5) (20). First-phase insulin secretion was considered the average incremental plasma insulin concentration from 2.5 to 10 min of the hyperglycemic clamp divided by the average incremental plasma glucose concentration during the same interval. Second-phase insulin release was taken as the average incremental plasma insulin concentration during the last hour of the hyperglycemic clamp divided by the average incremental plasma glucose concentrations during the same interval. Insulin sensitivity was assessed by using HOMA-IR, calculated as (fasting plasma insulin [pmol/l] × fasting plasma glucose [mmol/l])/135 (20) and directly determined by dividing the average glucose infusion rate during the last hour of the hyperglycemic clamp by the average plasma insulin concentration during the same interval (referred to as the insulin sensitivity index [ISI]) (19). The ISI was multiplied by the ratio of 180 mg/dl to the actual plasma glucose concentration (in milligrams per deciliter) during the hyperglycemic clamp to account for small differences in glycemia. In healthy individuals with normal glucose homeostasis, a decrease in insulin sensitivity is fully compensated for by an increase in insulin secretion, so that the product of both of these processes, referred to as the disposition index (DI), remains constant (11). We therefore evaluated the appropriateness of β-cell function in relation to insulin sensitivity by calculating the DI of the first- and second-phase insulin response by multiplying the respective insulin responses by the ISI (11).

Statistical analyses

BMI, waist-to-hip ratio (WHR), fasting plasma insulin, HOMA-%B, HOMA-IR, first- and second-phase insulin responses, ISI, and the DIs were log transformed to obtain a normal distribution of the data for statistical analyses. Since our primary goal was to compare the pathophysiology of IFG and IGT, data were compared among the NFG/NGT, IFG/NGT, and NFG/IGT groups. Data of the IFG/IGT group were used to test for interaction between IFG and IGT. Continuous variables were compared among groups using ANOVA followed by the least-significant-difference test for variables for which the *F* test was significant; categorical variables, i.e., sex, were compared using the χ^2 test. Metabolic parameters were compared among the NFG/NGT, IFG/NGT, and NFG/IGT groups with and without adjustments for age, sex, BMI, and WHR. Normally distributed variables are given as means ± SD. For skewed data, geometric means and 95% CIs are given. All analyses were conducted using SAS (version 9.1.2; SAS Institute, Cary, NC). *P* values <0.05 were considered statistically significant.

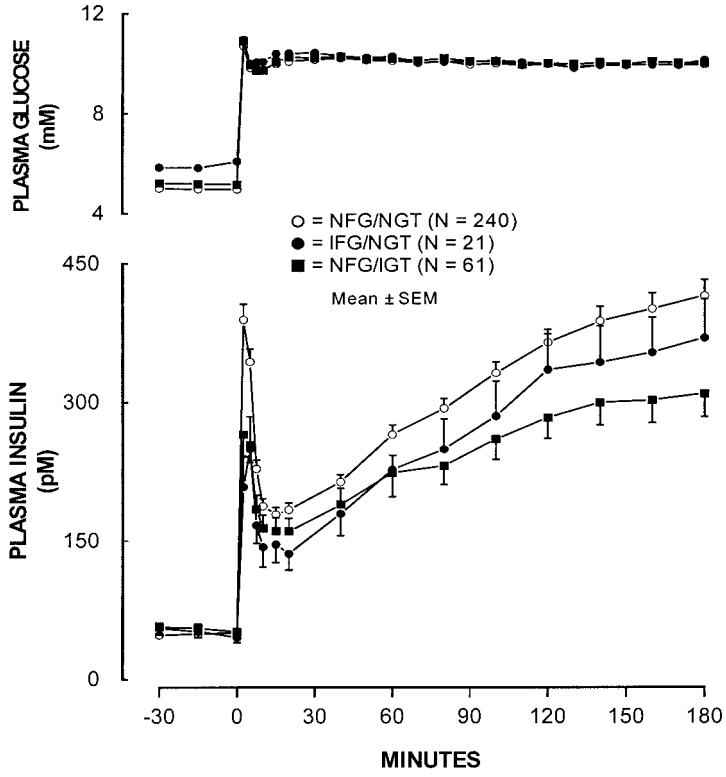

Figure 1—*Plasma concentrations of glucose and insulin during the hyperglycemic clamp in subjects with NGT (NFG/NGT), isolated IFG (IFG/NGT), or isolated IGT (NFG/IGT).*

RESULTS — Age, sex, BMI, and WHR were significantly different among the NFG/NGT, IFG/NGT, and NFG/IGT groups, as indicated by ANOVA and χ^2 tests (all $P < 0.01$). Compared with the NFG/NGT subjects (age 40.4 ± 11.8 years, $n = 64$ men and 176 women, BMI 25.9 kg/m^2 [95% CI 25.5–26.4], and WHR 0.81 [0.80–0.82]), IFG/NGT (age 45.0 ± 9.7 years, $P = 0.08$) and NFG/IGT (age 47.0 ± 12.1 years, $P < 0.0001$) subjects were older, IFG/NGT ($n = 11/10$, $P = 0.013$) but not NFG/IGT ($n = 20/41$, $P > 0.3$) subjects had a greater male-to-female ratio, NFG/IGT (27.7 kg/m^2 [26.5–28.9], $P < 0.003$) but not IFG/NGT (26.6 kg/m^2 [25.1–28.2], $P > 0.4$) subjects had a greater BMI, and IFG/NGT (0.88 [0.85–0.91]) and NFG/IGT (0.85 [0.83–0.88]) subjects had a greater WHR (both $P < 0.0001$). None of the physical characteristics were, however, significantly different between the IFG/NGT and NFG/IGT groups.

Fasting glycemia and glucose tolerance

By definition, fasting plasma glucose concentrations were greater in the IFG/NGT group (5.82 ± 0.25 mmol/l) than in the NFG/NGT (4.89 ± 0.35) and NFG/IGT groups (5.16 ± 0.25) (both $P < 0.0001$), and 2-h postchallenge plasma glucose concentrations were greater in the NFG/IGT group (8.81 ± 0.80 mmol/l) than in the NFG/NGT (5.75 ± 1.05) and IFG/NGT groups (6.15 ± 1.17) (both $P < 0.0001$). Nevertheless, fasting plasma glucose concentrations were slightly but significantly greater in the NFG/IGT than the NFG/NGT group ($P < 0.0001$).

Hyperglycemic clamp

ANOVA indicated significant differences among the NFG/NGT, IFG/NGT, and NFG/IGT groups for HOMA-%B, first-phase plasma insulin response, second-phase plasma insulin response, ISI, both DIs (all $P < 0.01$), and HOMA-IR ($P < 0.05$). Baseline plasma insulin concentrations were not significantly different among the three groups despite the fasting hyperglycemia in the IFG/NGT subjects (Fig. 1 and Table 1).

Accordingly, compared with the NFG/NGT group, HOMA-%B was decreased ~35% in the IFG/NGT group ($P < 0.002$), indicating impaired basal insulin secretion, but was not reduced in the NFG/IGT group ($P > 0.5$). HOMA-IR was significantly increased in the IFG/NGT group (by ~30%, $P < 0.05$) but not the NFG/IGT group ($P = 0.11$) (Table 1).

During the hyperglycemic clamp, plasma glucose increased to comparable levels in all groups ($P > 0.6$) (Fig. 1). Compared with the NFG/NGT group, both the IFG/NGT and NFG/IGT groups had ~30% reduced first-phase insulin responses ($P < 0.018$ and <0.0003, respectively). In contrast, NFG/IGT but not IFG/NGT subjects had significant decreases in second-phase insulin responses (by ~30%, $P < 0.0001$) and the ISI (by ~15%, $P < 0.03$) (Fig. 1 and Table 1). Accordingly, in IFG/NGT subjects, the DI of the first-phase insulin response was reduced ~30% ($P < 0.006$) and the DI of the second-phase insulin response was normal ($P > 0.4$), whereas in NFG/IGT subjects, both DIs were reduced ~40–50% (both $P < 0.0001$) (Table 1).

Adjustment for age, sex, BMI, and WHR had little influence on baseline plasma insulin concentrations, HOMA-%B, and first- and second-phase plasma insulin responses; therefore, the statistical results of these parameters remained similar (Table 2). Adjustment for age and sex also had little influence on HOMA-IR and the ISI (data not shown). However, after further adjustment for BMI and WHR, HOMA-IR ($P > 0.5$) and the ISI were no longer significantly different among the

Table 1—*Results from the hyperglycemic clamp test*

	NFG/NGT*	IFG/NGT†	NFG/IGT‡	*P* * vs. †	*P* * vs. ‡	*P* † vs. ‡
Fasting plasma insulin (pmol/l)	43.7 (40.8–46.8)	44.4 (35.0–56.2)	49.0 (42.5–56.4)	>0.9	0.15	>0.4
HOMA-%B ([pmol/l]/[mmol/l])	97.3 (89.9–105)	62.0 (49.9–76.9)	91.9 (79.3–107)	<0.002	>0.5	<0.012
Insulin secretion						
First phase ([pmol/l]/[mmol/l])	38.9 (35.8–42.2)	26.4 (19.3–36.1)	26.7 (22.7–31.4)	<0.018	<0.0003	>0.9
Second phase ([pmol/l]/[mmol/l])	59.0 (54.5–63.9)	65.1 (50.7–83.8)	40.7 (34.1–48.7)	>0.5	<0.0001	<0.005
HOMA-IR ([pmol/l] × [mmol/l])	1.53 (1.42–1.65)	1.98 (1.59–2.47)	1.75 (1.51–2.03)	<0.05	<0.11	>0.4
ISI (μmol · kg^{-1} · min^{-1} per pmol/l)	0.139 (0.129–0.149)	0.136 (0.107–0.174)	0.116 (0.097–0.138)	>0.8	<0.03	>0.3
DI						
First phase (μmol · kg^{-1} · min^{-1} per mmol/l)	5.42 (5.03–5.83)	3.60 (2.45–5.29)	3.09 (2.64–3.62)	<0.006	<0.0001	>0.3
Second phase (μmol · kg^{-1} · min^{-1} per mmol/l)	8.24 (7.83–8.68)	8.88 (7.22–10.9)	4.72 (4.28–5.20)	>0.4	<0.0001	<0.0001

Data are geometric means (95% CI).

NFG/NGT, IFG/NGT, and NFG/IGT groups, suggesting that the differences in insulin sensitivity were largely due to differences in obesity.

Comparisons between the IFG/NGT and NFG/IGT groups and interaction between IFG and IGT

When subjects with isolated IFG and isolated IGT were compared with one another, the IFG group had greater reductions in basal β-cell function as assessed by HOMA-%B (~−35 vs. −5%, $P < 0.012$), comparable reductions in first-phase insulin release (both ~−30%, $P > 0.9$), and less reductions in second-phase insulin release (~+10 vs. −30%, $P < 0.005$) and the DI of the second-phase insulin response (~+8% vs. −45%, $P < 0.0001$). Differences in HOMA-IR, the ISI, and the DI of the first-phase insulin response did not reach statistical significance (Table 1). The statistical results remained similar after adjustment for age, sex, BMI, and WHR (Table 2).

There was no significant interaction between IFG and IGT (all $P > 0.2$), such that their associated defects in insulin secretion and action were additive in subjects with IFG/IGT (data not shown).

CONCLUSIONS — The present study was undertaken to compare the pathophysiology of IFG and IGT in a more comprehensive and standardized fashion than has hitherto been done by assessing basal insulin release and first- and second-phase insulin release, as well as insulin sensitivity, in a large number of individuals with isolated IFG, isolated IGT, or combined IFG and IGT and in healthy control subjects, using the hyperglycemic clamp technique. We found that *1*) in isolated IFG, basal insulin secretion and glucose-stimulated first-phase insulin secretion are impaired but second-phase insulin secretion and (peripheral, mainly representing muscle) insulin sensitivity are normal; *2*) in isolated IGT, basal insulin secretion is normal but glucose-stimulated first- and second-phase insulin secretion and (peripheral) insulin sensitivity are reduced; and *3*) there is no significant interaction between IFG and IGT, such that their associated defects in insulin secretion and sensitivity are additive in individuals who have combined IFG and IGT. These results hence support previous suggestions (3–10) that IFG and IGT are distinct metabolic abnormalities.

Our findings are consistent with those from most but not all previous studies that insulin resistance, as assessed by FSIVGTTs or euglycemic clamps, plays a lesser role in IFG than IGT (3,4,7). In con-

Table 2—*Results from the hyperglycemic clamp test, adjusted for age, sex, BMI, and WHR*

	NFG/NGT*	IFG/NGT†	NFG/IGT‡	*P* * vs. †	*P* * vs. ‡	*P* † vs. ‡
Fasting plasma insulin (pmol/l)	48.8 (45.3–52.5)	44.1 (34.8–55.8)	48.1 (41.8–55.3)	>0.8	0.10	>0.4
HOMA-%B ([pmol/l]/[mmol/l])	104 (96–113)	60.3 (48.6–74.7)	88.3 (76.3–102)	<0.0007	>0.5	<0.007
Insulin secretion						
First phase ([pmol/l]/[mmol/l])	39.9 (36.7–43.3)	26.9 (19.6–36.8)	26.3 (22.3–30.9)	<0.013	<0.0002	>0.9
Second phase ([pmol/l]/[mmol/l])	64.5 (59.5–70.0)	64.5 (50.2–82.9)	40.2 (33.7–48.1)	>0.4	<0.0001	<0.002
HOMA-IR ([pmol/l] × [mmol/l])	1.68 (1.53–1.84)	1.90 (1.55–2.34)	1.67 (1.46–1.91)	§	§	§
ISI (μmol · kg^{-1} · min^{-1} per pmol/l)	0.121 (0.112–0.131)	0.134 (0.105–0.171)	0.120 (0.101–0.143)	§	§	§
DI						
First phase (μmol · kg^{-1} · min^{-1} per mmol/l)	4.87 (4.54–5.21)	3.62 (2.46–5.33)	3.15 (2.68–3.70)	<0.005	<0.0001	>0.3
Second phase (μmol · kg^{-1} · min^{-1} per mmol/l)	7.90 (7.51–8.32)	8.69 (7.08–10.7)	4.83 (4.38–5.32)	>0.4	<0.0001	<0.0001

Data are geometric means (95% CI). §Not statistically significant (by ANOVA).

trast, when evaluated by HOMA-IR, individuals with IFG were found to be at least similarly, if not more, insulin resistant than individuals with IGT in the present and most previous studies (3,5,6,8–10). These apparent contradictory findings may be due to a bias of HOMA-IR toward finding lower insulin sensitivity in individuals with IFG, since their increased fasting plasma glucose concentrations contribute to an increase in HOMA-IR. Alternatively, it is possible that HOMA-IR, FSIVGTTs, and euglycemic as well as the present hyperglycemic clamps measured different processes.

In the fasting state, insulin regulation of EGP is the major factor determining plasma glucose concentrations, since most tissue glucose uptake occurs by insulin-independent mechanisms (2). HOMA-IR, which is solely based on fasting plasma glucose and insulin concentrations, may therefore primarily be an index of the resistance of hepatic and renal glucose release to suppression by insulin (21), whereas the studies using FSIVGTTs or glucose clamp experiments (3,4,7) probably primarily measured the ability of insulin to stimulate muscle glucose uptake.

With respect to β-cell function, we found that basal insulin release was impaired in IFG but not IGT individuals, as indicated by the lack of increased plasma insulin concentrations despite fasting hyperglycemia and decreased HOMA-%B. This observation is consistent with all HOMA-%B data of earlier similar studies (6–8). In contrast to basal insulin release, first-phase insulin responses were comparably reduced in IFG and IGT in the present study, as has been found in one (4) but not the other (3) prior study using FSIVGTTs. Furthermore, we found that second-phase insulin responses were reduced in IGT but not IFG; this had not been previously examined.

Regarding the differences in pathophysiologies between IFG and IGT, our results indicate that decreases in first-phase insulin responses were not involved, as first-phase insulin responses were comparably reduced in both groups. The fact that basal insulin release was decreased in IFG but not IGT suggests that impaired basal insulin release may be an important element in the pathogenesis of IFG. Conversely, the fact that second-phase insulin responses were reduced in IGT but not IFG suggests that impaired second-phase insulin release may be an important element in the pathogenesis of IGT. Furthermore, our data indicate that there may be differences in hepatorenal and muscle insulin sensitivity between IFG and IGT that may be critical factors.

As mentioned above, HOMA-IR largely reflects resistance of glucose production by liver and kidney to suppression by insulin, whereas hyperglycemic clamp–determined insulin sensitivity largely reflects the sensitivity of muscle glucose uptake to stimulation by insulin (22). Our finding that in IFG, HOMA-IR was increased but hyperglycemic clamp–determined insulin sensitivity was not decreased lead us therefore to postulate that in IFG individuals, there may be selective or preferential hepatorenal insulin resistance. The observation that in overnight-fasted IFG Pima Indians, rates of EGP were increased despite increased plasma insulin concentrations supports this hypothesis (4). Conversely, our finding that in IGT, hyperglycemic clamp–determined insulin sensitivity was reduced but HOMA-IR was not increased suggests that in IGT individuals, there may be preferential insulin resistance in muscle.

Accordingly, considering the abnormalities in insulin sensitivity and β-cell function, the present study suggests that in IFG, reduced hepatorenal insulin sensitivity, combined with impairments in basal insulin secretion and first-phase insulin release, causes fasting hyperglycemia, whereas in IGT, peripheral insulin resistance, combined with impairments in first- and second-phase insulin responses, causes postprandial hyperglycemia. Expressed differently, normal or near-normal second-phase insulin responses and muscle insulin sensitivity may prevent IFG individuals from having postprandial hyperglycemia. In contrast, normal or near-normal basal insulin release and hepatorenal insulin sensitivity may prevent IGT individuals from having fasting hyperglycemia.

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