Pathogenic Factors Responsible for Glucose Intolerance in Patients With NIDDM

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To define the pathogenic factors responsible for glucose intolerance in NIDDM, we estimated insulin secretory capacity, S_I, and S_G in 11 healthy, nondiabetic subjects and 9 NIDDM patients who had no S_I impairment. All subjects studied were nonobese and normotensive. Each underwent a 75-g OGTT and a modified FSIGT: glucose was administered (300 mg/kg body weight), and insulin was infused (20 mU/kg over 5 min) from 20 to 25 min after the administration of glucose. S_I and S_G were estimated by Bergman's minimal-model method. The insulin response to oral glucose was significantly lower in NIDDM patients than in normal control subjects. First-phase insulin secretion expressed as the integrated area of plasma insulin above the basal level during the first 20 min was much smaller in NIDDM subjects (214 ± 112 pM · min) than in control subjects (4643 ± 885 pM · min, $P < 0.01$). S_I was not statistically different in normal control subjects ($1.27 \pm 0.18 \times 10^{-4}$ $min^{-1} \cdot pM^{-1}$) versus diabetic patients ($1.62 \pm 0.33 \times 10^{-4}$ $min^{-1} \cdot pM^{-1}$). However, S_G was significantly lower in diabetic subjects ($1.11 \pm 0.17 \times 10^{-2}$ min^{-1}) than in control subjects ($2.35 \pm 0.26 \times 10^{-2}$ min^{-1}, $P < 0.01$). These results suggest that impaired insulin secretion and decreased S_G are the factors responsible for glucose intolerance of Japanese NIDDM patients with normal insulin sensitivity. Because S_I and S_G are the factors responsible for glucose intolerance of NIDDM patients with insulin resistance, it is conceivable that decreased S_G is common in NIDDM patients regardless of their S_I index. *Diabetes* 41:1540–46, 1992

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NIDDM, non-insulin-dependent diabetes mellitus; S_I, insulin sensitivity; S_G, glucose effectiveness; OGTT, oral glucose tolerance test; FSIGT, frequently sampled i.v. glucose tolerance test; ICA, islet cell antibody; ICSA, islet cell surface antibody; WHR, waist-to–hip girth ratio; CV, coefficient of variation; G(t), plasma glucose concentration; I(t), plasma insulin concentration; Gb, base-line concentration of plasma glucose; Ib, base-line concentration of plasma insulin; X(t), time course of peripheral insulin effect; K_g, rate of glucose disappearance; IDDM, insulin-dependent diabetes mellitus; S_GO, glucose effectiveness at 0 insulin.

Glucose tolerance depends on a complex interaction between insulin secretion from β-cells and the actions of insulin to accelerate glucose disappearance and inhibit endogenous glucose production (S_I). An additional factor, less well recognized, is the ability of glucose per se, independent of changes in insulin, to increase glucose uptake and suppress endogenous output (glucose effectiveness). These factors can be measured in the intact organism with physiologically based Bergman's minimal models of glucose utilization and insulin kinetics (1,2). Furthermore, administration of insulin permits minimal-model analysis to be applied to diabetic as well as normal subjects (3,4).

Recently, Welch et al. (4), using a modification of the minimal-model method, reported that S_G was significantly reduced in NIDDM patients with insulin resistance. According to the computer simulation, Bergman (2) found no single defect in any individual factor—as much as 80% reduced from normal—was sufficient to reduce K_g to a diabetic value ($K_g < 1.0$). In contrast to single defect, combined defects were severely synergistic in reducing glucose tolerance. Thus, S_I and S_G reduction together would result in a diabetic tolerance value.

NIDDM, however, is a heterogeneous disorder. Banerji and Lebovitz (5) described two subpopulations of NIDDM subjects, one with primary insulin deficiency and normal insulin action and the other with primary peripheral insulin resistance and a mild impairment in glucose-mediated insulin secretion. Arner et al. (6) also reported that NIDDM patients with abdominal obesity displayed peripheral insulin resistance in combination with defec-

TABLE 1
Clinical characteristics of normal subjects and NIDDM patients

	Sex	Age (yr)	BMI (kg/m^2)	WHR	Fasting glucose (mM)	Fasting insulin (pM)	HbA_{1c} (%)	Family history of diabetes	Duration (mo)
Normal subjects									
1	F	20	21.4	0.681	4.83	39.9	—	No	—
2	F	21	20.0	0.761	4.72	42.2	—	No	—
3	F	22	20.4	0.721	5.38	52.9	—	No	—
4	F	22	22.7	0.736	5.55	50.4	—	No	—
5	F	20	21.1	0.681	4.61	53.2	—	No	—
6	F	22	19.8	0.744	4.83	51.2	—	No	—
7	M	22	23.6	—	5.61	58.0	—	No	—
8	M	22	21.0	—	5.16	34.1	—	No	—
9	M	23	18.4	—	5.22	43.0	—	No	—
10	M	22	20.2	—	4.94	18.3	—	No	—
11	M	25	20.8	—	4.66	19.1	—	No	—
Mean ± SE		21.9 ± 0.4	20.9 ± 0.4	—	5.05 ± 0.11	42.0 ± 4.1	—	—	—
NIDDM patients									
1	F	58	21.2	0.799	6.72	48.8	6.2	Yes	2
2	F	54	18.3	0.750	5.72	18.2	6.6	No	12
3	F	50	19.2	0.808	5.66	36.5	6.5	Yes	5
4	F	58	23.0	0.886	5.51	61.0	8.7	Yes	3
5	M	25	18.8	0.810	5.27	24.2	6.9	No	12
6	M	50	19.8	0.900	9.16	35.6	8.8	Yes	1
7	M	39	18.6	0.915	8.38	25.3	6.2	Yes	24
8	M	43	16.0	0.854	7.33	26.0	9.9	Yes	1
9	M	49	24.5	0.922	5.18	56.3	7.8	Yes	1
Mean ± SE		47.3 ± 3.5*	19.9 ± 0.9	—	6.55 ± 0.48*	36.9 ± 5.1	7.5 ± 0.4	—	6.8 ± 2.6

*$P < 0.01$ vs. normal subjects.

tive insulin secretion, whereas nonobese diabetic patients showed only a secretory defect. Thus, NIDDM subjects may fall into two groups, between which the cause of glucose intolerance differs.

It has not yet been investigated whether decreased S_G occurs in NIDDM subjects with normal S_I. Therefore, this experiment used a modification of the minimal-model method to assess S_G and S_I and insulin secretory capacity in NIDDM patients who had no impairment in S_I. Subjects with normal glucose tolerance who had no family history of diabetes served as control subjects.

RESEARCH DESIGN AND METHODS

Twenty nonobese Japanese subjects (11 normal, nondiabetic subjects [5 men, 6 women] and 9 NIDDM patients [5 men, 4 women]) were studied. Glucose tolerance was estimated according to the 1979 National Diabetes Data Group criteria (7). Subjects with plasma glucose levels >11.1 mM both at 120 and at 30, 60, or 90 min after glucose load were considered to have diabetes (Table 1, Fig. 1). Their ages ranged from 20 to 58 yr. Fink et al. (8) showed that S_I was not altered in the subjects 20–59 yr old. The urine of the diabetic subjects was free of ketones. Both ICAs and ICSAs measured by the method of Irvine et al. (9) and Lernmark et al. (10), respectively, were negative in all diabetic subjects studied. No diabetic subjects had been treated previously with insulin or any oral hypoglycemic agents. They were receiving diet therapy alone. The duration of diabetes was 6.8 ± 2.6 mo (Table 1). All subjects studied were nonobese and normotensive, and had normal renal, hepatic, and thyroid functions. None of the participants in this study consumed alcohol or performed heavy exercise for at least 1 wk before the test. For at least 3 days before the test, their body weights and daily diets were stable. They did not take any medications known to alter carbohydrate metabolism. They had no family history of hypertension or obesity. There was a positive family history of diabetes mellitus in 7 patients with NIDDM. Normal subjects had no family history of diabetes. Women were studied in the follicular phase of the menstrual cycle except for 4 diabetic subjects past menopause, aged 50–58 yr. Before their participation, the nature, purpose, and risks of the study were explained to all subjects, and their informed written consent was obtained. Subjects were weighed clothed without shoes. Measurements of the waist at the smallest abdominal circumference and the hips at the largest gluteal circumference were used to determine WHR (11).

All subjects underwent a 75-g OGTT and a FSIGT. Tests were performed in random order at least 3 days apart. Subjects were given 75 g of glucose orally in the morning after an overnight fast. Blood samples were obtained from an antecubital vein before and 30, 60, 90, and 120 min after glucose load for the analysis of glucose and insulin.

After an overnight fast, butterfly needles were inserted into the antecubital veins and were maintained by a slow drip of physiological saline. Subjects were allowed to rest quietly for at least 15 min before blood sampling. Baseline samples for glucose and insulin were obtained at −20, −10, and −3 min. Glucose was administered i.v. (300 mg/kg body weight) within 2 min, and subsequent samples were obtained from the contralateral antecubital

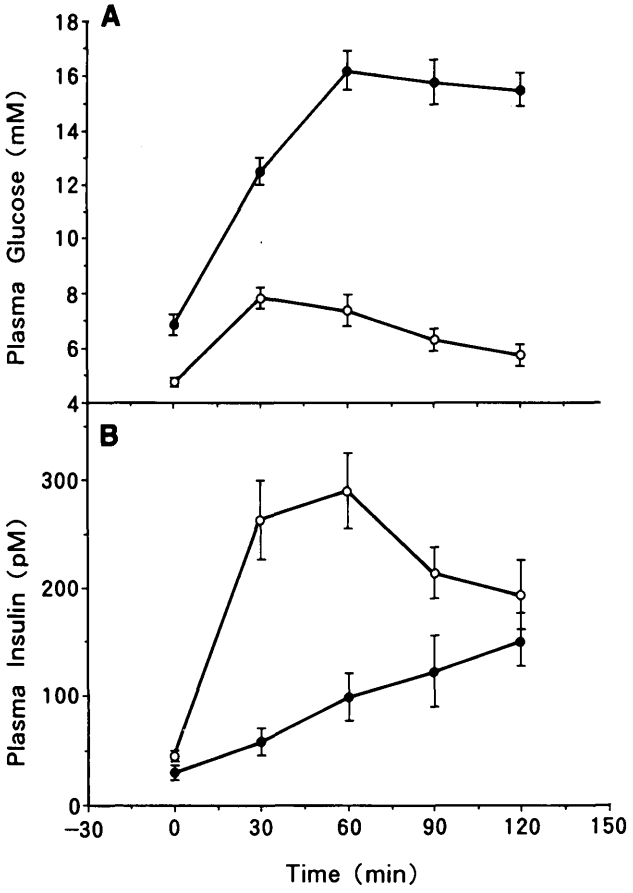

FIG. 1. Plasma glucose (*A*) and plasma insulin (*B*) concentrations during 75-g OGTT for normal subjects (○—○) and NIDDM patients (●—●). Plasma glucose levels were significantly higher in diabetic subjects than in normal subjects at all times during the test. Plasma insulin levels were lower in diabetic patients, but a significant difference was observed at 30, 60, and 90 min after glucose administration. Values are means ± SE.

vein at frequent intervals until 180 min, as described previously (3). Plasma was frozen and stored at −20°C for later analysis. Insulin (Humalin R, Shionogi, Osaka, Japan) was infused (20 mU/kg over 5 min) into an antecubital vein from 20 to 25 min after the administration of glucose (3).

Analytical methods. Plasma glucose was measured in triplicate spectrophotometrically with glucose oxidase (Glucose B-test, Wako Pure Chemical Industries, Osaka, Japan). The measurement error of glucose was assumed to be normal distribution of zero mean, and with a CV of 1.5%. Immunoreactive insulin was measured in duplicate using a Phadeseph insulin RIA kit (Shionogi). CVs were 4% for insulin >180 pM and 7% for insulin <180 pM.

Data analysis. K_g value was calculated as the slope of the least-square regression line relating the natural logarithm of the glucose concentration to time from at least four samples drawn between 10 and 20 min and between 20 and 40 min.

S_I and S_G were estimated by the minimal-model approach (1–4). In this analysis, fluctuations in circulating glucose levels over time are described by the differential equations $dG(t)/dt = -p1[G(t) - Gb] - X(t)G(t)$ and $dX(t)/dt = -p2X(t) + p3[I(t) - Ib]$ where G(t) is the plasma glucose concentration, I(t) is the plasma insulin concentration and Gb and Ib are baseline concentrations. X(t) represents the time course of peripheral insulin effect. Parameter p1 represents the effect of glucose per se, at basal insulin, to normalize its own concentration in plasma independent of increased insulin. This parameter is known as S_G and has been verified through comparison with studies in which the insulin secretory response was suppressed (12). The ratio of p3 to p2 defines the S_I index, which represents the increase in the net K_g dependent on a rise in insulin above basal. Index S_I has been validated by comparison with a direct measure of S_I from glucose clamp experiments in both humans (13,14) and dogs (15). Because S_G reflects the ability of glucose to mediate its own disposal and suppress basal hepatic glucose production at basal insulin level, we calculated S_G at 0 insulin as $S_G - (S_I \times Ib)$, where Ib is basal insulin level (16).

The minimal-model program was written in Pascal (Borland International, Scotts Valley, CA) on a Macintosh IIcx (Apple Computer, Cupertino, CA). The Marquardt-Lebenberg method was used for nonlinear least-square estimation of the parameters, and the systems of differential equations were solved using a fourth-order Runge-Kutta integration algorithm (17). In particular, source programs (mrqmin and rk4) supplied by Press et al. (18) were adapted to the particular situation of the minimal models. Step size for the integration was 1 min (17). Immediately after glucose injection, the pattern of plasma glucose is dominated by extracellular mixing. Because the minimal model assumes a single well-mixed glucose pool, these early data points must not be taken into account for the minimal-model analysis. Therefore, the values at 0–8 min were zero-weighted, as suggested by Pacini and Bergman (17).

Precision of parameter estimates was evaluated using a covariance matrix, as described previously (17,18), and expressed as fractional SD. Mean ± SE of the fractional SDs of p1, p2, and p3 in 20 subjects were 15.3 ± 2.5, 18.4 ± 2.6, and 12.9 ± 1.5%, respectively, and were comparable with published results (17).

Endogenous plasma insulin responses were expressed both as peak insulin levels achieved during the first 20 min after the administration of glucose and as the area under the insulin curve 0–20 min after the administration of glucose. The integrated area of plasma insulin above their basal level was calculated using the trapezoidal method (18).

Statistics. Data are mean ± SE. To evaluate differences between patients with NIDDM and normal subjects, data were analyzed by Student's *t* test, with the level of statistical significance at $P < 0.05$.

RESULTS

Clinical characteristics of the subjects at the time of study are presented in Table 1. The patients with NIDDM were older (47.3 ± 3.5 yr) than the normal control subjects (21.9 ± 0.4 yr). BMI of the patients with NIDDM (19.9 ± 0.9 kg/m^2) was similar to that of control subjects (20.9 ± 0.4 kg/m^2). The WHRs for normal female sub-

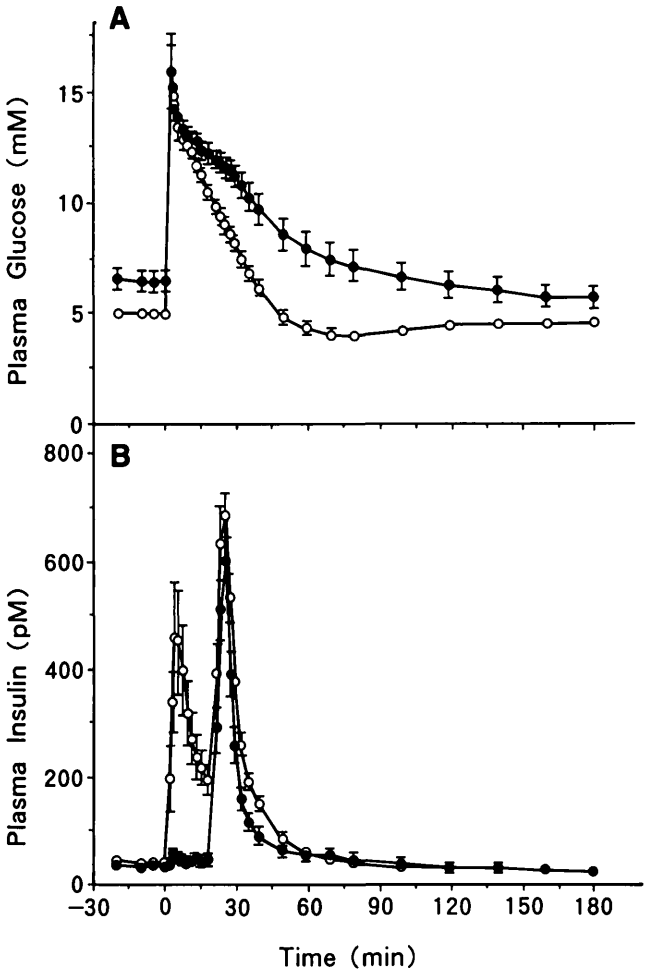

FIG. 2. Plasma glucose (*A*) and plasma insulin (*B*) concentrations during modified FSIGT for normal subjects (○—○) and NIDDM patients (●—●). Plasma glucose levels of NIDDM patients were significantly higher than those of normal subjects from 14 to 180 min. Plasma insulin levels of NIDDM patients were significantly lower than those of normal subjects from 3 to 19 min and from 28 to 40 min. Values are means ± SE.

jects were 0.721 ± 0.014 (range 0.681–0.761); WHRs for NIDDM female and male patients were 0.811 ± 0.028 (range 0.750–0.886) and 0.880 ± 0.021 (range 0.810–0.922), respectively.

OGTT. Plasma glucose levels were significantly higher in diabetic patients than in nondiabetic control subjects at all times during the test (Fig. 1). Plasma insulin levels were lower in diabetic patients, but significant differences were observed at 30, 60, and 90 min after glucose administration.

Modified FSIGT. Plasma glucose and insulin concentrations during modified FSIGT are charted in Fig. 2. Basal glucose levels were significantly higher in diabetic patients (6.55 ± 0.48 mM) than in control subjects (5.05 ± 0.11 mM) (Table 1). Administration of glucose immediately increased plasma glucose concentrations to 15.9 ± 1.7 mM in control subjects and to 16.0 ± 1.1 mM in diabetic patients. During the first 10 min, plasma glucose levels of both groups decreased similarly, and no statistically significant difference in glucose concentrations was observed between the two groups. During the next 10 min, from 10 to 20 min, K_g was significantly lower in NIDDM patients (0.72 ± 0.21%/min) than in control subjects (2.19 ± 0.20%/min) (Table 2). From 14 min to 180 min, the difference in plasma glucose concentration between the two groups was statistically significant. During the 20 min from 20 to 40 min, K_g was significantly lower in NIDDM patients (1.24 ± 0.24%/min) than in control subjects (2.73 ± 0.22%/min; $P < 0.01$), although K_g accelerated in both groups after insulin infusion at 20 min. At 50 min, mean plasma glucose level of control subjects returned to the basal level, whereas that of the NIDDM patients was still higher than the basal level. It took a longer time for NIDDM patients (109 ± 14 min) to reduce plasma glucose back to basal level than it took control subjects (55 ± 3 min; $P < 0.01$).

Plasma insulin concentration of control subjects increased immediately after glucose administration, but that of NIDDM patients remained close to basal level until exogenous insulin infusion began at 20 min. The integrated area of plasma insulin above the basal level during the first 20 min was much smaller in NIDDM patients (214 ± 112 pM · min) than in control subjects (4643 ± 885 pM · min) (Table 2). Insulin infusion produced a peak in plasma insulin concentration in both groups at 25 min. After insulin infusion, plasma insulin level of NIDDM patients was slightly lower than that of control subjects, and the difference was statistically significant at 28–40 min.

Minimal-model analysis. S_I in control subjects and NIDDM patients was 1.27 ± 0.18 × 10^{-4} min^{-1} · pM^{-1} and 1.62 ± 0.33 × 10^{-4} min^{-1} · pM^{-1}, respectively, and there was no statistically significant difference between the two groups. S_G in the NIDDM patients (1.11 ± 0.17 × 10^{-2} min^{-1}) was significantly lower than that in control subjects (2.35 ± 0.26 × 10^{-2} min^{-1}). S_G at 0 insulin also was significantly lower in NIDDM patients (0.60 ± 0.14 × 10^{-2} min^{-1}) than in control subjects (1.83 ± 0.27 × 10^{-2} min^{-1}) (Table 2).

DISCUSSION

This study attempted, using a modification of the minimal-model method, to define the pathogenic factors responsible for glucose intolerance in NIDDM patients with normal S_I. Several clinical studies have revealed that most patients diagnosed with NIDDM are insulin resistant (19–23). However, Banerji and Lebovitz (5), Chaiken et al. (24), and Arner et al. (6) reported that NIDDM patients consisted of two subpopulations—one with primary insulin deficiency and normal insulin action and the other with primary peripheral insulin resistance and a mild impairment in glucose-mediated insulin secretion. Our NIDDM patients had no impairment in S_I, as assessed by the minimal-model method (Table 2). Note that the S_I values found in the control subjects were similar to values reported in the literature (2–4,12–14,25,26). They were characterized by significantly reduced insulin responses to both oral and intravenous glucose (Figs. 1, 2; Table 2). Kosaka et al. (27) previously demonstrated decreased insulin response to oral glucose in nonobese Japanese diabetic patients regardless of the degree of glycemic

TABLE 2
Metabolic parameters of normal subjects and NIDDM patients

	$S_I \times 10^4$ ($min^{-1} \cdot pM^{-1}$)	$S_G \times 10^2$ (min^{-1})	$S_GO \times 10^2$ (min^{-1})	Insulin peak* (pM)	Insulin area† (pM × min)	Peak insulin‡ (pM)	K_g§ (%/min)
Normal subjects							
1	1.52	1.67	1.06	340	2745	644	1.50
2	0.69	3.84	3.55	451	5044	768	2.75
3	0.80	2.76	2.34	686	5806	652	2.02
4	2.31	2.24	1.08	222	1952	619	1.49
5	1.88	2.49	1.49	314	2318	610	3.43
6	0.61	1.72	1.41	557	5325	893	2.24
7	1.05	3.71	3.10	1372	11729	1132	2.71
8	0.86	1.10	0.81	399	4797	605	1.18
9	1.24	1.64	1.11	394	3061	832	2.10
10	0.87	2.24	2.08	699	6862	820	2.36
11	2.13	2.46	2.05	174	1436	864	2.29
Mean ± SE	1.27 ± 0.18	2.35 ± 0.26	1.83 ± 0.27	510 ± 100	4643 ± 885	767 ± 49	2.19 ± 0.19
NIDDM patients							
1	1.07	0.46	0.00	64	194	633	−0.35
2	1.06	1.23	1.04	78	626	582	0.82
3	2.24	1.10	0.28	83	344	623	1.24
4	0.66	1.39	0.99	115	801	755	0.95
5	1.89	1.35	0.89	59	−33	765	1.10
6	0.91	0.34	0.02	34	−188	454	−0.26
7	2.14	0.94	0.40	24	−53	613	0.68
8	3.72	1.98	1.01	51	−64	446	1.28
9	0.88	1.24	0.74	131	303	755	1.07
Mean ± SE	1.62 ± 0.33	1.11 ± 0.17‖	0.60 ± 0.14‖	71 ± 12‖	214 ± 112‖	625 ± 40	0.73 ± 0.20‖

*Insulin peak before insulin administration.
†Insulin area between 0 and 20 min after glucose administration.
‡Insulin peak after insulin administration.
§Glucose disappearance rate between 10 and 20 min after glucose administration in IVGTT.
‖$P < 0.01$ vs. normal subjects.

control. Ratzmann et al. (28) reported that the majority of nonobese patients with glucose intolerance and relative insulin deficiency do not exhibit a reduced responsiveness to insulin. Therefore, hypoinsulinemia, but not insulin resistance, is the primary defect for an abnormal tolerance in our subjects.

Our newly diagnosed NIDDM patients are unique in that they were mild diabetic (fasting glucose 6.55 ± 0.48 mM) Japanese with normal fasting insulin level and were not obese (BMI = 19.9 ± 0.9 kg/m^2). Interestingly, no significant difference was observed in fasting glucose and insulin levels between our patients and the NIDDM patients with normal S_I studied by Banerji and Lebovitz (5). Only two reports studying S_I in Japanese NIDDM patients are available: Harano et al. (29) showed that 7 of 79 NIDDM subjects had normal S_I assessed by a technique using glucose, insulin, and somatostatin infusion. Okamoto et al. (30) measured S_I by euglycemic clamp. In their 10 diabetic patients, 5 had normal S_I. However, their patients had higher fasting glucose and insulin levels than our NIDDM patients. Chaiken et al. (24) showed normal S_I in 12 of 30 black NIDDM subjects (by euglycemic clamp).

Minimal-model analysis also permitted estimation of S_G (1–4). We found that S_G was significantly lower in NIDDM patients ($1.11 \pm 0.17 \times 10^{-2}$ min^{-1}) than in control subjects ($2.35 \pm 0.26 \times 10^{-2}$ min^{-1}) (Table 2). S_G is the total effect of glucose on fractional glucose disappearance independent of an increase in insulin, but including the contribution of basal insulin. Therefore, we calculated S_G at 0 insulin as $S_G - (S_I \times Ib)$. S_G at 0 insulin also was significantly lower in NIDDM patients ($0.60 \pm 0.14 \times 10^{-2}$ min^{-1}) than in control subjects ($1.83 \pm 0.27 \times 10^{-2}$ min^{-1}) (Table 2).

It may be argued that aging itself impairs S_G because in our study, subjects with NIDDM were older than control subjects (Table 1). It seems, unlikely, however, because Chen et al. (25) and Pacini et al. (26) reported that S_G was not influenced by age. One might argue that the reduced S_G in NIDDM patients was accompanied by glucose intolerance. This also seems unlikely because Finegood et al. (3) found that S_I was reduced in poorly controlled IDDM and normalized in well-controlled patients. S_G, however, was found to be reduced in all IDDM subjects regardless of the degree of control.

According to the computer simulation proposed by Bergman (2), we examined the relative importance of individual and compound defects in β-cell function, S_I, and S_G on K_g (Fig. 3). Data shown in Fig. 3 are computer simulated, based on the measurements of S_G, S_I, and β-cell function from healthy individuals. S_I, S_G, and/or time course of plasma insulin concentration of normal subjects were replaced by mean value(s) of diabetic subjects, and the time courses of plasma glucose were plotted. K_g was evaluated between 10 and 20 min. No individual defect of these factors caused diabetic glucose tolerance, but combined defects were severely synergistic in reducing glucose tolerance. S_G reduction

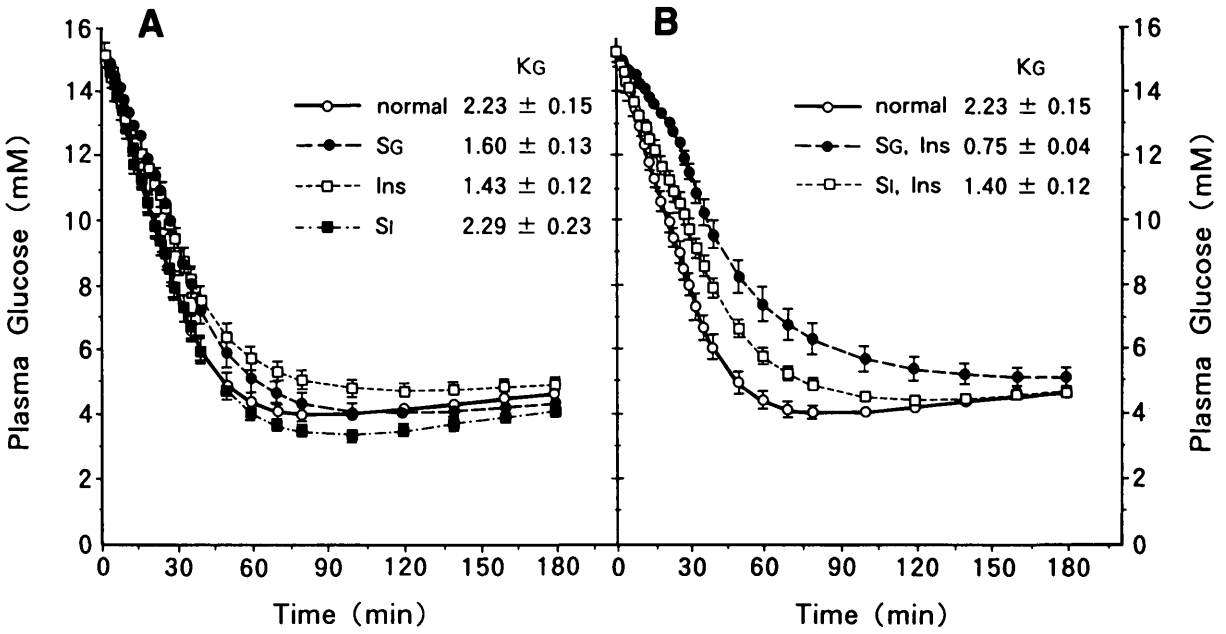

FIG. 3. Contribution of relative metabolic defects to glucose tolerance. With computer simulation of real data, we examined effects of individual (*A*) or combined defects (*B*) in S_G, β-cell function, and S_I on K_g. S_I, S_G, and/or time course of plasma insulin concentration of normal subjects was replaced by mean value(s) of diabetic subjects, and the time courses of plasma glucose were plotted. K_g value was calculated between 10 and 20 min. No individual defect of these factors caused diabetic glucose tolerance, but combined defects were severely synergistic in reducing glucose tolerance. S_G reduction and β-cell dysfunction together would result in diabetic tolerance. Values are means ± SE.

and β-cell dysfunction together would result in diabetic tolerance, although simulation of the blood glucose regulating system may not be a perfectly accurate representation of glucose regulation in vivo.

NIDDM patients studied by Welch et al. (4) were insulin resistant. S_I of the NIDDM patients studied in these experiments was not different from that of control subjects. S_G was significantly reduced in NIDDM patients with normal S_I in this study and in those with insulin resistance studied by Welch et al. (4). Therefore, it may be possible that decreased S_G is a common finding in NIDDM patients regardless of S_I.

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