Administration of Sulfonylureas Can Increase Glucose-Induced Insulin Secretion for Decades in Patients With Maturity-Onset Diabetes of the Young

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OBJECTIVE— To ascertain whether the effect of sulfonylureas on glucose-mediated insulin release persists for years to decades in patients with maturity-onset diabetes of the young.

RESEARCH DESIGN AND METHODS— The effect of sulfonylurea treatment on glucose-induced insulin secretion was ascertained prospectively for up to 33 yr in 12 diabetic patients of the maturity-onset diabetes of the young RW pedigree, who are genetically homogeneous because they share DNA markers on chromosome 20q. In 7 of these patients, paired glucose tolerance tests, given while the patients were on and off sulfonylureas, were performed after 7–31 yr.

RESULTS— Glucose-induced insulin secretion showed an average increase of 68% in diabetic patients who remained responsive to chlorpropamide after having been on and off the drug for decades. In most patients, however, glucose-induced insulin secretion declines over time (1–4%/yr). Some patients become unresponsive to sulfonylureas after 3–25 yr and then have very small or no increases in glucose-induced insulin secretion and require treatment with insulin to normalize fasting hyperglycemia.

CONCLUSIONS— Increase in glucose-induced insulin secretion remains the most important mechanism of the action of sulfonylureas during long-term administration.

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MODY, maturity-onset diabetes of the young; OGTT, oral glucose tolerance test; NIDDM, non-insulin-dependent diabetes mellitus; FPG, fasting plasma glucose; GTT, glucose tolerance test; G-6-PD, glucose-6-phosphatase dehydrogenase; IRI, immunoreactive insulin; RIA, radioimmunoassay; AUC, area under the curve; MAX, maximal values of the curve; BMI, body mass index; df, degrees of freedom.

The acute effects of sulfonylurea drugs in stimulating the secretion of insulin from the pancreatic β-cells have been documented repeatedly in studies performed in normal and diabetic patients, in animals, and in vitro (1–3). More than 30 years after the introduction of sulfonylurea drugs for the treatment of NIDDM, controversy remains over whether chronic sulfonylurea therapy results in increased insulin secretion.

As reviewed by Lebowitz (1), several studies that compared concentrations of plasma insulin during OGTTs before and after administration of sulfonylurea drugs for 4 to 200 wk in NIDDM patients reported glucose-mediated insulin secretion as unchanged, decreased, or increased. Most studies have reported unchanged or decreased plasma levels of immunoreactive insulin associated with decreased FPG and postglucose plasma glucose levels after chronic administration of sulfonylureas. Thus, some investigators have postulated that a major mechanism by which sulfonylureas exert their chronic antidiabetic effect is through potentiation of insulin action rather than a measurable increased secretion of insulin (1–3). Lebowitz summarized that "the bulk of data currently available in the literature does not support the concept that the improvement in glycemic control occurring during chronic sulfonylurea therapy can be attributed primarily to an increase in the quantity of insulin secreted" (1). On the other hand, both Gerich (2) and Groop (3) concluded that long-term treatment of NIDDM patients results in continuously augmented insulin secretion because administration of sulfonylureas for periods of up to 12 mo enhanced basal and glucose-stimulated insulin secretion, while FPG levels and glucose tolerance were improved (3–6).

No reported studies have ascertained the effect of sulfonylureas on glucose-mediated insulin secretion in NIDDM patients after treatment has ex-

ceeded 4 yr; in most studies, sulfonylureas have been administered for weeks to months.

In this study, we describe the effect of sulfonylureas, administered for up to 33 yr, on glucose-induced insulin secretion in diabetic patients with MODY of the RW pedigree who have been followed prospectively while being treated with such drugs (7). MODY is defined as NIDDM in the young (identified before 25 yr of age and frequently between 9–13 yr of age) plus autosomal dominant inheritance. Among diabetic members of the RW pedigree, ~80% had fasting hyperglycemia at diagnosis or follow-up, and ~30% became insulin requiring on follow-up (7,8). Typical severe micro- and macroangiopathic complications occur in some members of this pedigree as in some patients with classical NIDDM (7,8).

Our results indicate that sulfonylureas can increase glucose-induced insulin secretion for decades in MODY patients who remain responsive to these drugs. In the majority of these patients, glucose-induced insulin secretion declines over time to varying degrees, which appears to represent the natural history of β-cell function in MODY of this pedigree. Some patients develop fasting hyperglycemia unresponsive to maximal doses of sulfonylureas after 3-25 yr and then have very small or no increases in glucose-induced insulin secretion and require treatment with insulin. This study indicates that an increase in glucose-induced insulin secretion remains the most important mechanism of the action of sulfonylureas during their long-term administration.

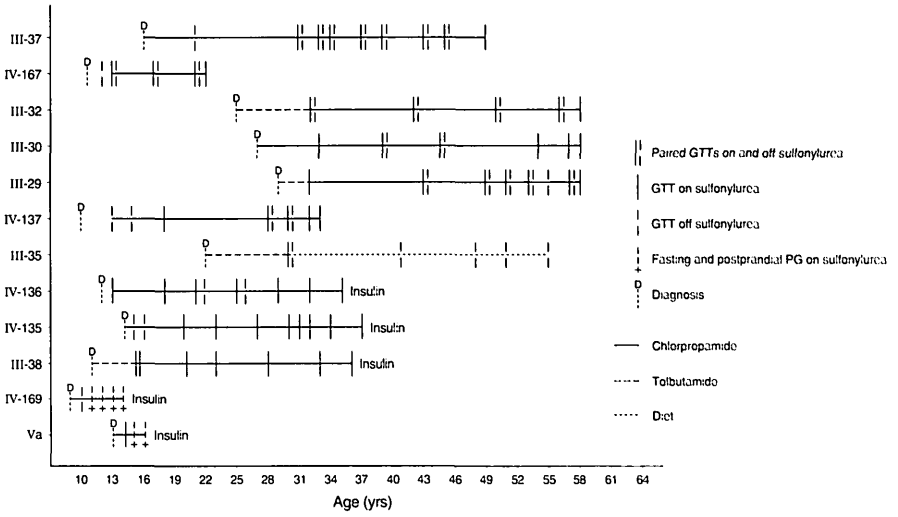

Figure 1—*Timing of the paired GTTs, as well as of unpaired tests, on and off sulfonylurea treatment during follow-up of the 12 MODY patients.*

RESEARCH DESIGN AND METHODS

— We studied 12 MODY members of the RW pedigree (Table 1) who are offspring of II-5 and are members of generations III, IV, and V (8). They are genetically homogeneous because they share DNA markers on chromosome 20q. The tightest linkage of the gene responsible for MODY of the RW pedigree is with the adenosine deaminase gene (9,10) and the D20S16 locus (11,12).

Diabetic patients were selected for this study if they could be followed prospectively with GTTs, performed while the patients were being treated with sulfonylurea drugs (primarily chlorpropamide) (Fig. 1). If fasting hyperglycemia could no longer be corrected with maximal dosages of sulfonylurea drugs, patients were treated with insulin and designated "insulin requiring."

The patients ranged in age from 9–29 (mean 16.4) yr and were diagnosed according to the NDDG criteria (13) in the course of routine testing because of a family history of diabetes. All were nonobese at diagnosis and during the follow-up studies (Table 1). Dosage of sulfonylureas was individualized according to FPG and postglucose or postprandial plasma glucose levels in an attempt to normalize the former, and if possible, the latter. Ten of these patients had been treated with sulfonylurea drugs for 8–33 (mean 24.2) yr; 3 became insulin requiring after 23, 25, and 25 yr, respectively. Two additional patients became insulin requiring after treatments with chlorpropamide for 3 and 4 yr, respectively.

In 6 patients treated with chlorpropamide for periods up to 7–31 (mean 20.5) yr, the results of 2–7 sets of paired GTTs are available: one test while the patient was taking the drug and the other after drug therapy had been discontinued for 3 wk (Fig. 1). In a 7th subject (III-35), a single pair of tests was available after 8 yr of treatment with tolbutamide, one test while receiving the drug and the other after the drug had been discontinued for two days. The timings of the paired tests on and off sulfonylurea therapy during the follow-up of the 7 patients are given in Fig. 1.

For the 6 patients with multiple sets of paired GTTs, 1–5 (mean 2.5) additional unpaired GTTs while on sulfonylurea therapy were performed, which extended their periods of observation on sulfonylureas for a total of 9–33 (mean 25) yr (Fig. 1).

In 5 additional patients (without paired tests), sulfonylurea therapy was effective in normalizing fasting hyperglycemia for periods of 3–25 yr, even though the agents were no longer effective in doing so thereafter (Table 1). All

Table 1—*Clinical characteristics of 12 MODY patients in study*

Subject generation number*	Diagnosis Age (yr)	Diagnosis FPG (mg/dl)	Diagnosis Year	Highest FPG on follow-up mg/dl	Highest FPG on follow-up Wk off drug (or on chlorpropamide)	Highest FPG on follow-up Year	BMI during yr sulfonylurea treatment (kg/m^2)	Duration of augmented insulin response (yr)	Unresponsive to sulfonylurea treatment after number years	Current treatment
III-37	16	112	1958	273	3	1987	19.9–22.9	33	No	Chlorpropamide
IV-167	11	119	1979	225	3	1989	17.3–18.3	10	No	Chlorpropamide
III-32	25	129	1958	212	3	1988	21.3–22.7	32	No	Chlorpropamide
III-30	27	238	1958	238	—	1958	25.1–26.1	17	No	Chlorpropamide
III-29†	29	167	1958	191	3	1988	21.9–22.7	28	No	Chlorpropamide
IV-137	9	91	1967	197	3	1986	22.4–23.6	17	No	Chlorpropamide
III-35	21	91	1958	143	On diet	1985	23.0–23.5	8	No	Diet
								Last Test		
IV-136	12	106	1967	230	3	1980	21.9–24.1	9	Yes-23	Insulin
IV-135	14	167	1967	203	On chlorpropamide	1990	20.9–21.6	13	Yes-25	Insulin
III-38	11	125	1958	223	On chlorpropamide	1983	21.2–22.4	—	Yes-25	Insulin
III-169	9	146	1985	220	On chlorpropamide	1989	21.0–24.3	—	Yes-4	Insulin
Va	13	132	1984	259	On chlorpropamide	1985	19.0–19.7	—	Yes-3	Insulin

*Reference 8.
†Died of cancer in 1988.

5 became insulin requiring. Multiple tests on and off sulfonylurea therapy were performed on 3 of these patients (Fig. 1).

Protocol

For the GTTs we used a dose of 1.75 g dextrose/kg ideal body weight. Ideal body weight was calculated from Metropolitan Life Insurance tables and treated as a constant after 25 yr of age. The concentration of plasma glucose was measured with the procedure of Worthington Biochemical Company (Freehold, NJ), based on the coupled-enzyme method of Slein (14), using hexokinase and G-6-PD, with modifications by Bonder and Meade (15). IRI was measured with a double antibody RIA (16). The least detection limit was 1.5 μU/tube, the intra-assay variation was 3.2%, and interassay variation 5.0%. For the time period of tests included, the antibody did not change, and two changes in insulin standards did not affect the magnitude of results reported.

Statistical analysis

We computed AUC with the trapezoidal rule. AUC and MAX were transformed to a logarithmic scale (base 10) before analysis. Because AUC and MAX measure the effect of interest, and to limit the number of comparisons, AUCs and MAXs were compared between conditions, rather than comparing levels at each timepoint on the insulin or glucose curve. Comparisons over time were computed with within-subject differences for patients with more than one GTT. The effect of time on drug therapy was assessed by computing the correlations between time on drug with AUC and MAX after adjusting for patient-to-patient differences; i.e., the correlations were calculated after subtracting the means for each patient. The percentage change/yr for AUC and MAX were computed as follows: the slope of log AUC and log MAX on time were estimated by linear regression after adjusting for patient-to-patient differences; the antilog of the appropriate slope minus 1.0 is the percentage change/yr for AUC and MAX.

RESULTS — Descriptive data for each of the 12 patients are presented in Table 1. Figure 2 plots the mean plasma concentrations of glucose and insulin for the first and the last paired GTTs in the 6 MODY patients, both while they were being treated with sulfonylurea drugs (on) and after short-term discontinuation of sulfonylureas (off). The first of the paired tests were performed after periods of treatment with sulfonylureas for 0.33–15 (mean 9.9) yr. The last of the paired tests were performed after periods of treatment of 7–31 (mean 20.5) yr.

For the 6 MODY patients, mean plasma glucose was only slightly above normal when they were on drug therapy for the first and last of the paired tests, respectively (Fig. 2). When on chlorpropamide therapy during the last tests, the mean 1-, 2-, and 3-h FPG levels were 84, 204, 163, and 110 mg/dl, respectively. In contrast, fasting hyperglycemia and a grossly diabetic GTT result occurred when drug therapy was discontinued for 3 wk (Fig. 2). Mean FPG was 205 mg/dl and mean 2-h postglucose plasma glucose was 404 mg/dl 3 wk after patients were taken off therapy for the last tests, while corresponding plasma glucose levels were 150 and 308 mg/dl, respectively, when the patients were temporarily off therapy for the first of the paired tests.

The patients' mean insulin re-

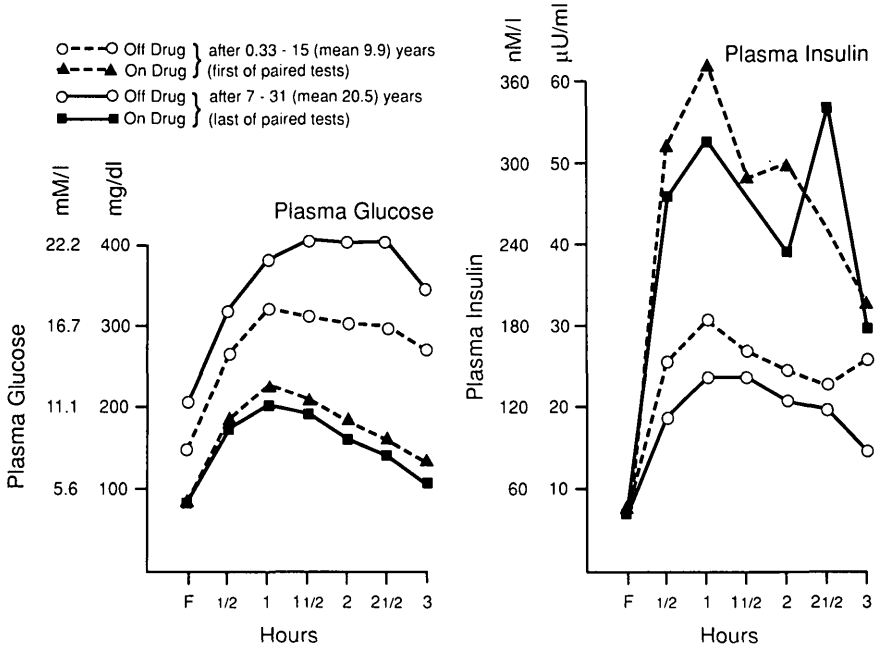

Figure 2—*Mean concentrations of plasma glucose and plasma insulin during OGTT in 6 MODY patients while on sulfonylurea therapy and after its short-term discontinuation (paired tests). For comparison, mean concentrations of plasma insulin during the 3-h GTT in 150 young (mean age 23.5 yr), nonobese, healthy control subjects were 10, 93, 103, 87, 73, 65, 45 μU/ml (17).*

sponse to glucose while off drug therapy was low compared with normal control subjects. The 6 patients who had multiple sets of paired GTTs had increases in plasma insulin from a mean fasting level of 7 μU/ml to a mean 1-h level of 31 μU/ml when drug therapy was discontinued for the first of the paired tests. Corresponding mean insulin levels were 8 and 24 μU/ml when chlorpropamide had been discontinued for the last of the paired tests. The 7th patient (III-35) with one set of paired tests had fasting and 1-h levels of 5 and 31 μU/ml when tolbutamide was discontinued for 2 days after 8 yr of its administration. (The other 5 patients had similar low increments in plasma insulin during the GTT when off drug therapy).

These increases contrast with the mean increment in plasma insulin during the GTT from a fasting level of 10 to 103 μU/ml at 1 h in 150 young (mean age 23.5 yr), nonobese, healthy control subjects who also were given 1.75 g glucose/kg ideal body weight (17). The mean low insulin response to glucose was augmented substantially while the patients were on sulfonylurea therapy (Fig. 2). The mean fasting and 1-h levels for plasma insulin for the 6 diabetic patients were 8 and 62 μU/ml for the first paired test, and 7 and 53 μU/ml for the last paired test. For subject III-35, fasting and 1-h insulin levels were 14 and 51 μU/ml on tolbutamide therapy.

To determine the significance of the differences in plasma glucose and plasma insulin for the paired tests shown in Fig. 2, we analyzed AUC and MAX. Both were significantly lower for glucose and higher for insulin when the patients were on drugs than when they were off ($P < 0.001$). The average decrease in AUC for glucose was 44% and in MAX, 42%. The average increase in AUC for insulin was 68% and in MAX, 66%.

In 5 of 6 patients, an augmented insulin response was apparent beyond the time of the last paired tests, when compared with an earlier test off chlorpropamide therapy. In patient III-37, an augmented insulin response on chlorpropamide was seen after 33 yr of therapy; in patient III-32, after 32 yr; in patient III-29, after 28 yr; in patient IV-137, after 17 yr; and in patient IV-167, after 10 yr (Table 1).

To determine the effect of known duration of diabetes and/or duration of drug therapy on concentrations of plasma glucose and insulin, partial correlations and change per year (slope) of AUC and MAX with time on drug were computed after adjusting for between-patient differences. The results are presented in Table 2.

Glucose

An increase in glucose over time was observed in AUC and MAX both for those on drugs and those off drugs. The increase for those off drugs was ~4.2%/yr ($P < 0.001$). For those on drugs who had paired tests, the increase was 1.3%/yr (did not achieve significance), but for the entire group the increase was 2.0%/yr ($P < 0.001$). The difference in rate of increase of AUC between those on drugs and those off drugs was significant ($P < 0.01$) for the paired tests. The high partial correlations are indicative of consistent relationships over time.

When the difference in glucose level between patients on drugs and off drugs (Δ) was correlated with time, the correlation was significant ($P < 0.01$ for AUC, $P < 0.02$ for MAX); i.e., the rates of increase differed between patients on drugs and those off drugs and were greater for those off drugs. When the first and last (chronological) tests were compared using a paired Student's *t* test, a significant change in Δ occurred over time (from a 15% increase when off drugs for the first pair of tests to an average 41% increase when off drugs for the last tests).

Table 2—*Partial correlation and change per year (slope) of AUC and MAX with time on drug adjusted for subject-to-subject differences*

	On/Off drug	n*	Slope (log scale)	Partial correlation	Student's t test	df	P value
Glucose							
AUC	Off	21	0.0183	0.799	5.143	15	0.001
AUC	Off	27	0.0178	0.750	4.808	18	0.001
AUC	On	21	0.0056	0.357	1.480	15	
AUC	On	58	0.0085	0.548	4.491	47	0.001
AUC	Δ†	21	−0.0127	−0.628	−3.123	15	0.01
MAX	Off	21	0.0177	0.780	4.824	15	0.001
MAX	Off	27	0.0172	0.738	4.639	18	0.001
MAX	On	21	0.0057	0.357	1.478	15	
MAX	On	58	0.0085	0.561	4.644	47	0.001
MAX	Δ†	21	−0.0120	−0.594	−2.861	15	0.02
Insulin							
AUC	Off	21	−0.0067	−0.509	−2.289	15	0.05
AUC	Off	27	−0.0067	−0.509	−2.509	18	0.05
AUC	On	21	−0.0040	−0.254	−1.015	15	
AUC	On	58	−0.0174	−0.679	−6.342	47	0.001
AUC	Δ†	21	0.0027	0.168	0.661	15	
MAX	Off	21	−0.0070	−0.446	−1.928	15	
MAX	Off	27	−0.0063	−0.380	−1.742	18	
MAX	On	21	−0.0035	−0.199	−0.787	15	
MAX	On	58	−0.0192	0.682	−6.387	47	0.001
MAX	Δ†	21	0.0035	0.145	0.568	15	

*Rows for which $n = 21$ contain the results for the 6 subjects with repeated paired sets of tests. The other rows report results for all subjects who had repeated tests even when paired on-drug and off-drug tests were not performed.

†Δ, Difference between off and on drug results correlated with time when paired OGTTs were evaluated.

Insulin

AUC decreased over time for both those patients off drugs and those on drugs. The decrease for those off drugs was ~1.5%/yr ($P < 0.05$). For those on drugs and who have paired tests, the decrease was 1.0%/yr (did not achieve significance), but for the entire group, the decrease while on drugs was 3.9%/yr ($P < 0.001$). The difference in the rate of decrease of AUC between those on drugs and those off drugs was not significant for the paired tests.

When the difference in insulin levels between on-drug and off-drug patients (Δ) is correlated with time, the correlation was not significant; i.e., the rates of decrease did not differ significantly between patients on drugs and those off drugs for those with paired tests. When the first and last (chronological) tests were compared using a paired Student's *t* test, no significant difference in Δ was found over time.

MAX had similar rates of decrease; the tests achieved statistical significance when all patients with repeated tests were used.

The magnitude of the changes in insulin concentration over time varied considerably among patients. Table 3 presents data from sequential GTTs in 6 patients with the largest decrease in insulin secretion with follow-up. In 3 patients (IV-136, IV-135, III-38) who were treated with up to maximal doses of sulfonylureas for 23–25 yr, large decreases in insulin secretion occurred (Table 3) and all became insulin requiring (Table 1). In 3 (III-30, III-29, IV-137) of the 6 patients who had multiple paired tests, a substantial further decrease in insulin secretion from the previous tests occurred 1–10 yr after the last of the paired tests (Table 3).

CONCLUSIONS— Our data indicate that long-term administration of sulfonylurea drugs substantially augment the glucose-induced increases in plasma levels of insulin (but not basal levels) by an average of 68%, for periods of up to more than three decades in patients with MODY of the RW pedigree. These increases in plasma insulin are undoubtedly attributable to augmented insulin secretion. This effect was evident in sets of paired GTTs given to 6 patients for periods of 7–31 yr. One test was performed while the patient was taking chlorpropamide daily, and the second test was administered when the drug had

Table 3—*Sequential glucose tolerance tests in 6 MODY patients who had substantial decreases in insulin levels with duration of sulfonylurea therapy*

Subject	Drug treatment (yr)	Chlorpropamide (mg)	Insulin (μU/ml)							Glucose (mg/dl)						
			0	0.5	1	1.5	2	2.5	3	0	0.5	1	1.5	2	2.5	3
IV-136	6	250	14	49	35	40	50	42	54	120	179	184	195	212	198	213
	20	500	4	11	14	10	15	13	12	110	194	277	329	368	392	396
IV-135	6	150	13	74	56	55	73	39	43	74	188	208	176	145	121	142
	23	450	11	14	13	15	16	15	12	201	302	306	520	498	573	461
III-38	3.5	Tolbutamide 1.5 g	11	17	20	21	47	17	10	93	164	202	161	139	92	76
	22	375	4	5	4	5	5	6	5	95	150	231	286	314	326	326
	25	500	1	—	2*	—	1*	—	—	223	—	318*	—	322*	—	—
III-30	12	500	4	31	44	47	64	30	30	88	240	324	349	296	192	116
	29	500	11	16	19	22	17	17	21	99	232	357	424	446	432	384
III-29	24	100	7	47	80	14	7	4	5	75	168	172	82	76	77	72
	28	100	4	15	28	15	9	7	7	74	202	251	145	157	132	119
IV-137	11.7	150	8	99	71	56	82	65	45	95	183	216	220	216	200	174
	18	200	10	39	49	50	30	26	23	102	219	312	301	329	292	246

*Postprandial breakfast.

been discontinued for periods of 3 wk (Fig. 1). In 5 of these patients an augmented insulin response to glucose was evident after an additional 1–4 yr while the patients were being treated with chlorpropamide beyond the time of the paired tests (Table 1). Thus, augmented insulin responses were seen after 10–33 (mean 22.8) yr in the 6 patients. In 3 of these patients an augmented insulin response was retained for more than 25 yr (i.e., after 33, 32, and 28 yr, respectively). In 2 patients, an augmented response was evident at the time of the last tests after 17 and 10 yr, respectively. In an additional 3 patients, an augmented insulin response persisted for 17, 13, and 9 yr, respectively, but was not apparent thereafter (Table 1).

The long duration of the effectiveness of chlorpropamide in augmenting glucose-induced insulin secretion makes it unlikely that the chronic administration of sulfonylureas usually leads to desensitization of the β-cell to the stimulatory effect of sulfonylureas on glucose-induced insulin secretion. Such an effect has been postulated as an important mechanism of secondary failures of sulfonylureas (18). Although it cannot be ruled out as a contributory mechanism, it is unlikely to be a primary or important one.

The increases in glucose-stimulated insulin levels with sulfonylurea therapy were associated with decreases in plasma glucose from fasting hyperglycemia and greatly elevated postglucose levels toward or into the normal range. After correction of hyperglycemia, no evidence was found of a return of the augmented insulin levels to the lower concentrations seen before the onset of sulfonylurea therapy, as has been reported in some studies (1–3). When sulfonylurea therapy was discontinued for 3 wk, the lower glucose-induced insulin concentrations were associated with higher FPG and postglucose plasma glucose concentrations. When the effect of sulfonylureas to augment insulin secretion declined appreciably with duration of therapy, greater postglucose hyperglycemia and eventually fasting hyperglycemia or progression in fasting hyperglycemia were found.

The results of these in vivo studies do not identify the mechanism by which sulfonylureas increase glucose-induced insulin secretion for prolonged periods of time. The mechanism for the acute effects of sulfonylureas on insulin release may persist after their prolonged administration for many years. Chronic chlorpropamide treatment likely increases the responsiveness of the β-cell to glucose (19) and improves the islet insensitivity to glucose characteristic of NIDDM (20).

The effects described in these patients with the MODY subtype of NIDDM are not specific for sulfonylureas. Similar increases in glucose-mediated insulin secretion occurred in patients with NIDDM and fasting hyperglycemia who were treated with one of three differing therapeutic regimens, each of which corrected fasting hyperglycemia and improved postglucose hyperglycemia: *1*) a reduction diet that caused weight loss; 2) exogenous insulin; and 3) sulfonylurea drugs (21). Because the three therapeutic regimens have differing effects on the β-cell and on insulin secretion, the reduction and normalization of FPG concentrations has been postulated to be related to the improvement in insulin secretion. Chronic elevations in concentration of plasma glucose in NIDDM patients may lead to progressive

impairment of insulin secretion (21), as well as to insulin resistance (22), a concept that has been designated as glucose toxicity (18).

In these studies, we could postulate that the normalization or improvement in plasma glucose and removal of glucose toxicity to the β-cell is the cause of the improvement in insulin secretion. Chlorpropamide, however, lost its effectiveness in decreasing hyperglycemia and in achieving fasting euglycemia after its chronic administration only when a progressive loss of a substantial drug-induced increment in plasma insulin occurred in response to glucose ingestion. Thus, metabolic control deteriorates with duration of diabetes only when there is a critical diminution of nutrient-stimulated insulin secretion. Without detracting from the general importance of the concept of glucose toxicity (see below) and its effect on insulin secretion and action, it appears that stimulation of increased insulin secretion is the most important or primary mechanism by which chronic administration of sulfonylureas continue to achieve euglycemia or near normal plasma glucose levels.

As documented above, the chronic administration of sulfonylureas is effective in augmenting glucose-induced insulin secretion and in correcting or improving hyperglycemia for more than three decades in some patients with MODY. Nevertheless, a decreased effectiveness of sulfonylureas on stimulation of glucose-induced insulin secretion with duration of known diabetes as well as with duration of sulfonylurea therapy was observed after periods of 3–27 yr. The 6 patients who had multiple paired GTTs on and off sulfonylurea therapy experienced a small but significant decrease of insulin secretion with duration of drug treatment of ~1–4%/yr. Of the 12 patients in this study, 5 lost their initial responsiveness to sulfonylureas in augmentation of insulin secretion and in control of fasting hyperglycemia after periods of 3–25 yr; they could be classified as secondary failures at those times.

Because postprandial hyperglycemia and even mild fasting hyperglycemia were not eliminated consistently by sulfonylurea therapy in these patients, glucose toxicity (i.e., a deleterious effect of hyperglycemia on β-cell function) may have been an important mechanism for the decreased insulin secretion with time. Nevertheless, if glucose toxicity is an important mechanism leading to decreases in the amplitude of insulin secretion and to secondary failures, the effectiveness of chronic sulfonylurea therapy in improving or correcting hyperglycemia for prolonged periods of time in these patients may have delayed the onset and progression of decreases in insulin secretion and the occurrence of secondary failures.

In summary, sulfonylureas can increase glucose-induced insulin secretion for decades in some MODY patients. Increase in glucose-induced insulin secretion remains the most important mechanism of sulfonylurea action during the drug's long-term administration. An additional extrapancreatic effect is likely. In the majority of these patients, glucose-induced insulin secretion declines over time to varying degrees (1–4%/yr), which appears to represent the natural history of β-cell function in this pedigree. A similar phenomenon may occur in some patients with classical NIDDM, particularly in those who are well controlled on sulfonylurea drugs for years and then become insulin requiring.

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