Gliclazide Potentiates Suppression of Hepatic Glucose Production in Non–Insulin-Dependent Diabetic Patients

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The mechanism of the hypoglycemic action of gliclazide was evaluated in 17 diet-treated non–insulin-dependent diabetes mellitus (NIDDM) patients. In study A, five patients received a 240-minute glucose infusion along with [3-^{3}H]glucose infusion. In study B, seven patients received a 240-minute isoglycemic insulin clamp along with [3-^{3}H]glucose infusion. And in study C, five patients received a somatostatin infusion with basal replacing doses of insulin and glucagon. The three studies (A, B, and C) were repeated twice. Gliclazide (240 mg orally) was administered on one occasion, and placebo was given on the second occasion. Basal hepatic glucose production (HGP) and utilization and plasma glucose, insulin, C-peptide, glucagon, and free fatty acid (FFA) concentrations were similar before administration of gliclazide and placebo. In study A, plasma glucose, its incremental area, and HGP were reduced by gliclazide administration (all $P < .05$), but glucose utilization was not significantly affected. The increase in plasma insulin and C-peptide concentrations was similar with gliclazide and placebo, although the plasma insulin to glucose ratio was increased with gliclazide. HGP decremental area was correlated with the reduction in plasma glucose incremental area ($r = -.63, P < .05$). In study B, gliclazide administration produced a larger suppression of HGP, but the overall rate of glucose utilization was not different in the two studies. In study C, plasma glucose concentration and HGP progressively decreased in both studies, without a difference between gliclazide and placebo. These results suggest that under conditions of hyperglycemia and hyperinsulinemia gliclazide elicits a larger suppression of HGP.

THE USE OF SULFONYLUREA agents has played a central role in the treatment of non–insulin-dependent diabetes mellitus (NIDDM) over the last 30 years. Despite such a large clinical experience, the mechanism(s) of action of these compounds remains to be fully elucidated. The first recognized action and possibly the most important was the ability to stimulate or potentiate glucose-mediated insulin secretion.[1] Moreover, an extrapancreatic action has been postulated for sulfonylurea drugs.[2] Such an extrapancreatic effect has received in vitro experimental support.[1,2] In vivo studies have shown that therapy with sulfonylurea agents can improve the insulin sensitivity of peripheral tissues and liver,[3-5] and it has been suggested that a major effect of sulfonylurea therapy in NIDDM is the suppression of hepatic glucose production (HGP).[3-6]

Still, it is difficult in those studies to determine what was a specific action of sulfonylurea on the liver and how much this effect was secondary to improved glucose control via more effective insulin secretion and relief of glucose toxicity.[7] Therefore, the present series of studies were undertaken to evaluate the acute effect, independently of chronic changes in plasma glucose levels, of pharmacological doses of gliclazide, a second-generation sulfonylurea agent, on hepatic glucose metabolism in NIDDM patients.

SUBJECTS AND METHODS

Subjects

Seventeen NIDDM patients were studied (Table 1). They were aged 52 ± 5 years and had a body mass index of 27.7 ± 0.5 kg/m^2. The mean duration of diabetes was 2.8 ± 1.9 years. All patients were on diet treatment, and no patient had received previous oral sulfonylurea drugs. None of the patients had clinical or laboratory evidence of hepatic, renal, or other endocrine disease. All patients were consuming a weight-maintaining diet containing at least 250 g carbohydrate per day for at least 1 week before the study. Before participating in the study, the purpose, nature, and potential risks were explained and each subject provided informed voluntary consent.

Study Protocol

Three studies were performed (A, B, and C). On the morning of each study following an overnight fast, a catheter was inserted into an antecubital vein for administration of test substances. A second catheter was inserted into the contralateral wrist vein, and the hand was placed in a heated box (60°C) for arterialized venous blood sampling. At 8 AM, a primed continuous (0.20 μCi/min) infusion of [3-^{3}H]glucose was started and maintained over a 3-hour equilibration period and for the duration of the study. The priming dose, which in normal subjects equals 100 times the rate of continuous infusion, in diabetic patients was increased in proportion to the fasting plasma glucose concentration. Blood samples were collected during the last 30 minutes of the tracer equilibration period for determination of plasma glucose, plasma glucose specific activity, and pancreatic hormones. After completion of the basal period, the protocol design was applied according to studies A, B, and C.

Study A. After collection of basal samples, 240 mg gliclazide (3 tablets) was administered orally to five subjects and a simultaneous intravenous (IV) glucose infusion (11.1 μmol/kg · min) was started. The same subjects underwent a repeat study with placebo administration. The studies were performed in random order. After beginning the glucose infusion, changes in plasma glucose, insulin, C-peptide, glucagon, and free fatty acid (FFA) concentrations were determined at 20-minute intervals for the next 4 hours. Infusions of glucose and [3-^{3}H]glucose were continued at a constant rate through the 4-hour period after gliclazide or placebo ingestion.

Study B. Seven patients participated in study B. After the basal period, they received 240 mg oral gliclazide or placebo in random order, and then a 240-minute isoglycemic insulin clamp study was performed. For this purpose, a primed continuous infusion (12 mU/m^2 · min) of regular insulin (Humulin R; Eli Lilly, Indianapo-

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Table 1. Clinical Characteristics of the Study Population

Subjects (N)	17
Sex (M/F)	8/9
Age (yr)	52 ± 5
Body mass index (kg/m²)	27.7 ± 0.5
Diabetes duration (yr)	2.8 ± 1.9
Glycated hemoglobin (%)	7.5 ± 0.7

lis, IN) was administered to acutely increase and maintain plasma insulin concentration at levels similar to those observed during study A. Plasma glucose concentration was then determined at 5- to 10-minute intervals, and a variable infusion of 20% dextrose was adjusted to maintain plasma glucose at the basal level.[8] During the insulin clamp, plasma [3-^{3}H]glucose specific activity was measured at 10-minute intervals.

Study C. In five subjects, after completion of a tracer equilibration period, 240 mg gliclazide was administered orally and a simultaneous infusion of somatostatin (250 μg/h), insulin (0.15 mU/kg · min), and glucagon (0.5 ng/kg · min) was begun and maintained constant for the next 4 hours. As for studies A and B, the five subjects were restudied with placebo. No glucose was infused in this set of studies. Plasma hormone and substrate concentrations and glucose specific activity were monitored at 20-minute intervals for the duration of the study.

Calculations

Basal HGP was determined by dividing the glucose infusion rate (dpm/min) by the steady-state plateau of [3-^{3}H]glucose specific activity (dpm/μmol/L) achieved during the last 30 minutes of the basal tracer infusion period. In the basal state, the rate of appearance (Ra) equals the rate of disappearance, and HGP and whole-body glucose utilization are thereby calculated.[9] After glucose infusion, a non–steady-state condition in glucose specific activity exists, and Ra and rate of disappearance were calculated by Steele's equations in their derivative forms.[10] The rate of endogenous glucose production (HGP) was calculated by subtracting the glucose infusion rate from the glucose Ra. Although errors in the calculation of HGP may be generated by changes in plasma [3-^{3}H]glucose specific activity, underestimation of HGP is unlikely in the present study, given the generally low rate of glucose metabolism.[10]

Analytical Procedures

Plasma glucose concentration was determined by the glucose oxidase method on a Beckman Glucose Analyzer II (Fullerton, CA). Methods for determination of plasma [3-^{3}H]glucose specific activity have been reported previously.[9] Plasma insulin, glucagon, and C-peptide concentrations were assessed by radioimmunoassay. Plasma FFA levels were measured by a microenzymatic method.[11]

Statistical Analysis

Data are presented as the mean ± SEM. Student's *t* test for paired observations was used to ascertain statistically significant differences.

RESULTS

Study A

Plasma glucose concentration and kinetics. Fasting plasma glucose concentration was not different on the morning of the study with gliclazide or placebo administration (Table 2). After starting the IV glucose infusion (11.1 μmol/kg · min), plasma glucose level increased by 3.4 ± 0.3 mmol/L above baseline (Fig 1) and slowly declined to 8.1 ± 0.7 mmol/L at the end of the study with placebo. Following administration of gliclazide (240 mg orally at time 0), both the maximal increase (2.1 ± 0.2 mmol/L; Fig 1) and plasma glucose at 240 minutes (6.7 ± 0.3 mmol/L) were significantly lower ($P < .05$). Accordingly, the incremental area above baseline was significantly lower when gliclazide was administered (352 ± 42 *v* 461 ± 52 mmol/240 min, $P < .05$).

Table 2. Basal Plasma Levels of Hormones and Substrates and Rate of HGP Before Studies With Gliclazide or Placebo

Parameter	Gliclazide	Placebo
Plasma glucose (mmol/L)	7.55 ± 0.7	7.35 ± 0.6
Plasma insulin (pmol/L)	78 ± 12	72 ± 15
Plasma glucagon (ng/L)	117 ± 7	106 ± 9
Plasma C-peptide (nmol/L)	0.58 ± 0.05	0.55 ± 0.06
Plasma FFA (mmol/L)	0.44 ± 0.04	0.46 ± 0.03
HGP (μmol/kg · min)	13.9 ± 1.0	13.8 ± 1.0

NOTE. Values represent the mean for all 17 patients participating in the 3 studies.

Figure 2 illustrates HGP and overall glucose utilization in the two experimental conditions. Whereas basal HGP was superimposable before gliclazide or placebo ingestion, HGP suppression during IV glucose loading was more pronounced with the former (−10.7 ± 1.1 μmol/kg · min) than with the latter (−6.7 ± 1.5 μmol/kg · min, $P < .05$). The decremental area under baseline HGP correlated with the incremental area in plasma glucose concentration ($r = .63$, $P < .05$; Fig 3). No apparent effect of gliclazide was found for overall glucose utilization (+7.4 ± 1.4 *v* +6.8 ± 0.9 μmol/kg · min; Fig 2).

Plasma hormone and FFA concentrations. Basal plasma levels of pancreatic hormones and FFAs were not different on the two study days. Both plasma insulin (+54 ± 6 pmol/L) and C-peptide (+0.40 ± 0.07 nmol/L) increased in response to IV glucose infusion (Fig 4). This increase did not differ when placebo (+54 ± 6 pmol/L and +0.43 ± 0.09 nmol/L plasma insulin and C-peptide, respectively) was administered. Ratios between the incremental area under the curve of plasma insulin, plasma C-peptide, and plasma glucose were calculated as indexes of β-cell sensitivity to

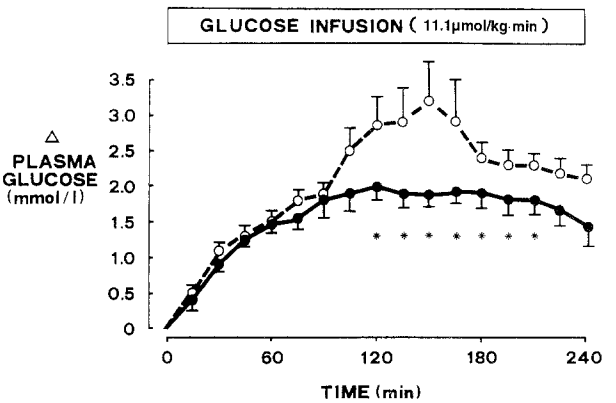

Fig 1. Plasma glucose increment above baseline following exogenous glucose infusion (11.1 μmol/kg · min) with gliclazide (●) or placebo (○) administration. *$P \leq .05$.

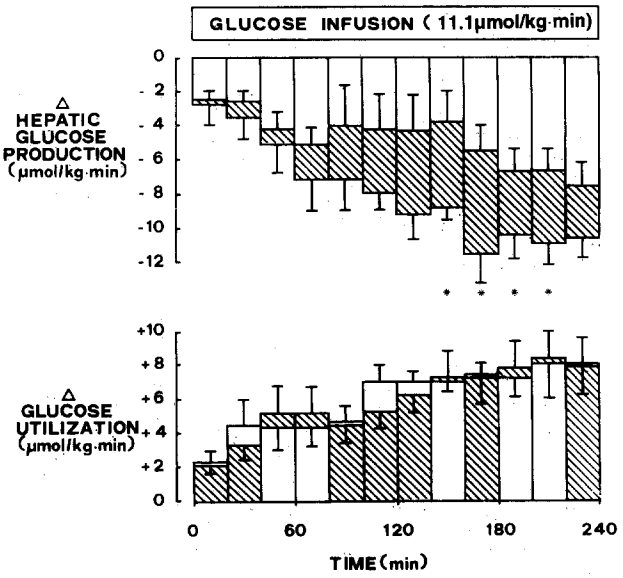

Fig 2. Absolute changes from baseline in the rate of HGP and glucose utilization following exogenous glucose infusion (11.1 μmol/kg · min) with gliclazide (▨) or placebo (□). *$P \leq .05$.

the ongoing glucose infusion. In each patient, gliclazide administration was associated with an increase of the plasma insulin to glucose and plasma C-peptide to glucose ratios (both $P < .01$; Fig 5).

Plasma glucagon (Fig 4) and FFA concentrations decreased with no difference between drug or placebo (glucagon, -18 ± 6, *v* -20 ± 6 ng/L; FFA, -0.21 ± 0.04 *v* -0.20 ± 0.06 mmol/L).

Study B

Since in study A significant albeit small differences in the portal plasma insulin concentration cannot be ruled out, a second study was designed in which insulin was infused at a rate known to suppress HGP without promoting significant peripheral glucose disposal. Under this experimental condition, plasma insulin was maintained at similar levels (172 ± 16 *v* 192 ± 12 pmol/L) with administration of both

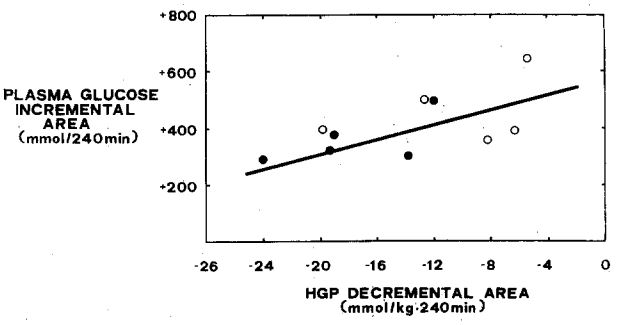

Fig 3. Linear regression ($r = .63, P < .05$) between the incremental area of plasma glucose concentration above baseline and the decremental area of HGP below baseline following exogenous glucose infusion (11.1 μmol/kg · min) with gliclazide (●) or placebo (○) administration.

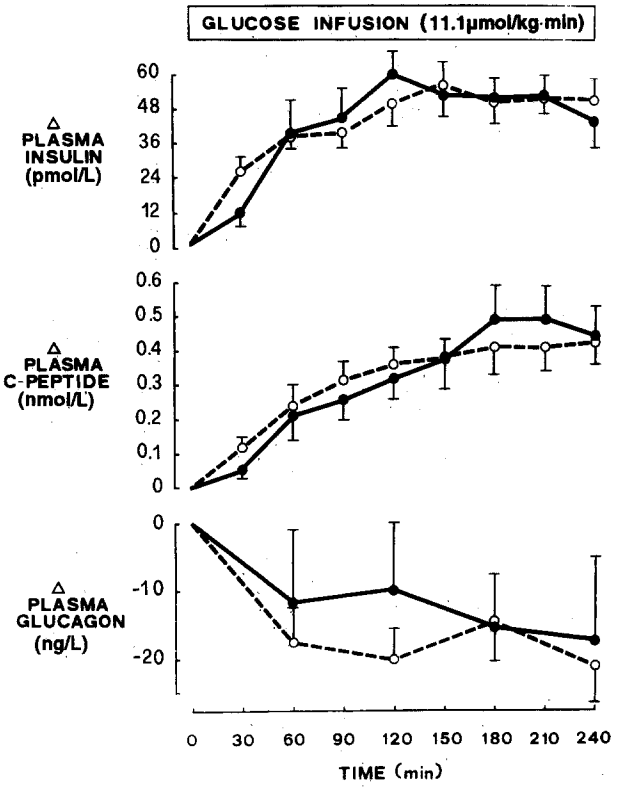

Fig 4. Absolute changes from baseline in plasma concentrations of insulin, C-peptide, and glucagon following exogenous glucose infusion (11.1 μmol/kg · min) with gliclazide (●) or placebo (○) administration.

gliclazide and placebo, while plasma glucose was kept constant at fasting plasma glucose concentration.

The basal plasma glucose level was not different (8.8 ± 1.1 *v* 8.6 ± 0.8 mmol/L) in the gliclazide and placebo studies, respectively. Similarly, no differences were found in basal HGP (12.6 ± 1 *v* 12.1 ± 1 μmol/kg · min, P = NS). During the insulin clamp study, plasma glucose was maintained at 8.4 ± 0.9 mmol/L with gliclazide and 8.1 ± 0.8 mmol/L with placebo with a coefficient of variation of $3.9\% \pm 0.4\%$ and $4.8\% \pm 0.8\%$, respectively. Under these controlled conditions, the overall rate of glucose utilization increased after administration of gliclazide or placebo (Fig 6), reaching similar figures during the last hour of the studies (21.1 ± 2.6 and 19.3 ± 2.8 μmol/kg · min, respectively, P = NS). Conversely, HGP decreased in both studies (Fig 6). However, in response to placebo, HGP declined to a lesser extent (2.9 ± 1.0 μmol/kg · min) than after gliclazide (0.6 ± 0.4 μmol/kg · min, $P < .05$) during the last hour of the isoglycemic insulin clamp. Plasma insulin (191 ± 21 *v* 209 ± 17 pmol/L) and C-peptide (0.39 ± 0.03 *v* 0.41 ± 0.04 nmol/L) concentrations were superimposable in the two studies (gliclazide and placebo, respectively).

Study C

In five diabetic individuals, gliclazide (240 mg orally) or placebo were administered at time 0, when a combined infusion of somatostatin, insulin, and glucagon was begun.

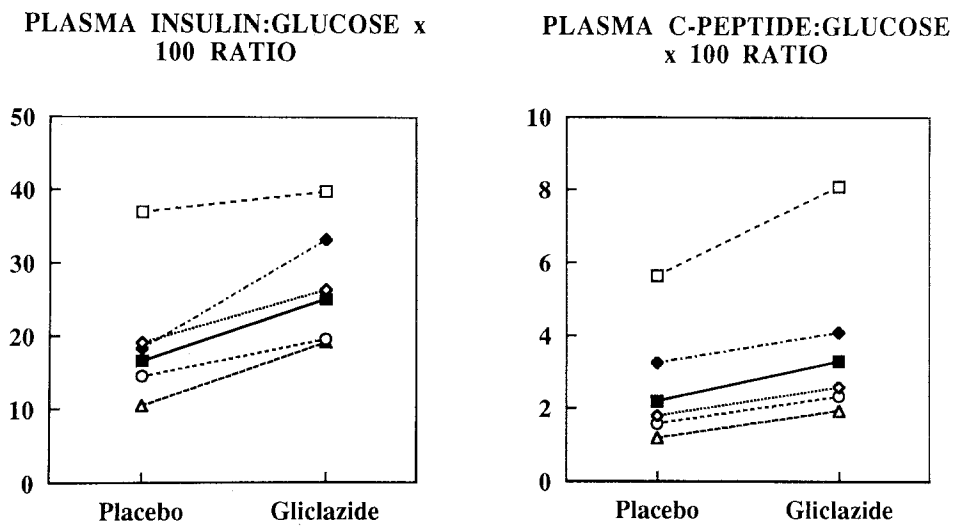

Fig 5. Individual ratios between the incremental areas of plasma insulin and plasma glucose concentrations and plasma C-peptide and plasma glucose concentrations during the 240-minute glucose infusion (2 mg/kg · min) with administration of placebo or gliclazide (240 mg orally).

As a consequence of the combined infusion, plasma C-peptide concentration was suppressed (gliclazide, 0.10 ± 0.01 nmol/L; placebo, 0.12 ± 0.02 nmol/L). Plasma insulin (72 ± 12 and 60 ± 6 pmol/L) and glucagon (115 ± 15 and 90 ± 12 ng/L) were maintained constant at basal levels (Fig 7). Under this condition, plasma glucose progressively declined following gliclazide (−2.2 ± 0.4 mmol/L) and placebo (−2.6 ± 0.4 mmol/L; Fig 8). The same trend was observed for HGP and glucose utilization (Fig 8).

DISCUSSION

Our results show that short-term administration of gliclazide, a second-generation sulfonylurea, to patients with NIDDM potentiates the suppression of HGP that follows IV glucose infusion in such patients. Nevertheless, this action seems to require the increase in plasma of either insulin or glucose concentrations.

When glucose was infused in patients taking gliclazide (240 mg orally), the zenith in plasma glucose concentration, the overall glucose profile (Fig 1), and the incremental area

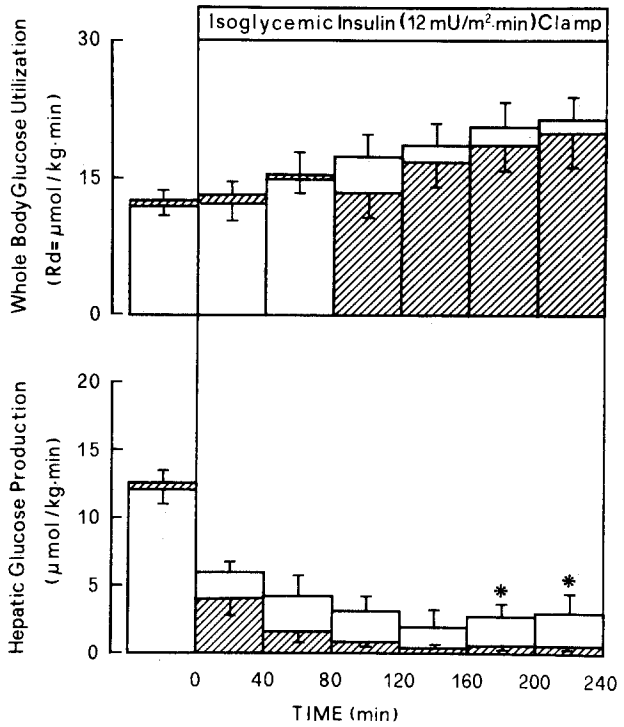

Fig 6. Glucose utilization and HGP during the isoglycemic (≈8.7 mmol/L) hyperinsulinemic (≈180 pmol/L) clamp study preceded by gliclazide (▨) or placebo (□) administration. *$P \leq .05$.

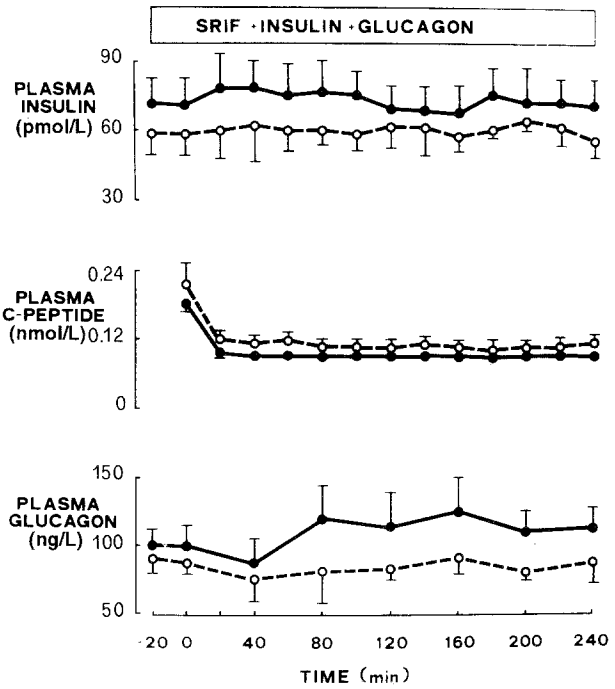

Fig 7. Absolute changes from baseline in plasma concentrations of insulin, C-peptide, and glucagon during combined infusion of somatostatin (250 μg/h), insulin (0.15 mU/kg · min), and glucagon (0.5 mU/kg · min) with gliclazide (●) or placebo (○) administration.

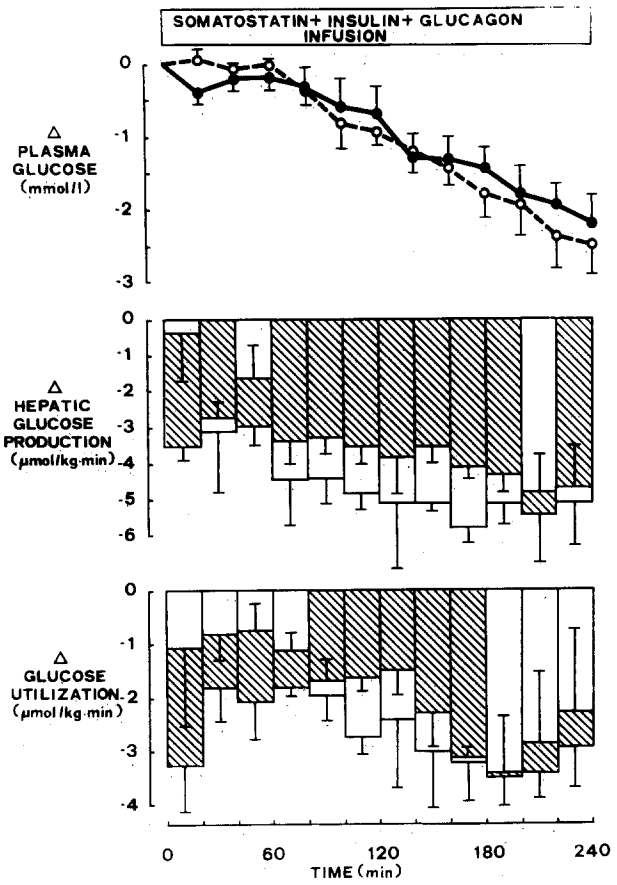

Fig 8. Absolute changes from baseline in plasma glucose concentration, HGP, and glucose utilization during combined infusion of somatostatin (250 μg/h), insulin (0.15 mU/kg · min), and glucagon (0.5 ng/kg · min) with gliclazide (●, ▨) or placebo (○, □).

were lower than in patients given placebo. This improvement in glucose tolerance was associated with a larger inhibition of HGP (Fig 2). Examination of the relationship between the incremental area of plasma glucose concentration above baseline and the decremental area of HGP indicates that a significant correlation ($r = .63$, $P < .05$) exists between the two variables. This strongly suggests that gliclazide action on HGP suppression is an important component of improved glucose tolerance in these patients. This finding is in agreement with previous reports[12-16] of long-term sulfonylurea treatment in NIDDM patients. In these studies, the reduction in fasting plasma glucose was associated with a proportional decline in basal HGP. Based on these observations, a specific effect of sulfonylurea agents on the liver was proposed.[3-6] Nevertheless, the hepatic effect of sulfonylurea agents may simply represent the effect of increased portal insulin concentration on the overall improvement in glucose metabolism with subsequent more efficient insulin action,[7] rather than a specific pharmacologic action on the liver.

The present study provides new evidence (1) that sulfonylurea agents, at least in pharmacologic doses, can directly act on hepatic glucose metabolism, and (2) that this HGP modulation may play a significant role in improving not only fasting plasma glucose concentrations but also postprandial hyperglycemia.

Following glucose infusion, the increase in plasma insulin and C-peptide did not differ with gliclazide or placebo. This was an unexpected finding, since the most prominent effect of sulfonylurea agents is stimulation of β-cell secretion.[1,2] Therefore, the finding of unchanged plasma insulin and C-peptide concentrations in the presence of the drug seems difficult to explain at first glance. Malaisse et al[13] showed that a feature of gliclazide action is modulation of insulin secretion as a function of glucose concentration. It is of note that plasma glucose was lower when gliclazide was used. In other words, lower glucose levels elicited an insulin response similar to that observed during the placebo study, when plasma glucose was higher. Accordingly, the plasma insulin to glucose and plasma C-peptide to glucose ratios were significantly higher (Fig 5), suggesting that gliclazide administration enhanced β-cell sensitivity to glucose. This observation is in keeping with the study by Matthews et al.[14] After a 3-week gliclazide therapy, they found a significant decrease in plasma glucose and a concomitant modest increase in plasma insulin, although improved β-cell function could be demonstrated in response to glucose and amino acids.

The timing of gliclazide administration also may explain, in part, the lack of a significant increase in both plasma insulin and C-peptide in response to glucose infusion. The plasma drug levels peak approximately 3 to 4 hours after ingestion.[12] In our study, the drug was administered immediately before starting the IV glucose infusion. Nevertheless, this effect might be offset by the pharmacologic dose (240 mg) used in the present study, since maximum plasma levels of the drug depend on the ingested dose.[12] Furthermore, it is of note that in our study the maximal effect on the liver occurred after the third hour of the study, despite a similar increment in plasma insulin concentration with the active drug or placebo (Figs 1 and 2). Finally, studies on the effect of the ingestion time of gliclazide in relationship to meals showed that administration of gliclazide 30 minutes before breakfast, immediately before breakfast, or 30 minutes after breakfast was not associated with significant differences in plasma glucose, insulin, or C-peptide concentrations.[17]

HGP is sensitive to small changes in portal insulin concentration.[18] Therefore, it would be sufficient for gliclazide to induce a modest improvement in β-cell secretion to induce a more evident effect on HGP. Such an interpretation is not supported by measurement of the plasma C-peptide concentration. C-peptide is not cleared by the liver,[19] so its measurement is a more reliable index of pancreatic insulin secretion into the portal stream. In our study, we did not detect any difference in plasma C-peptide levels between gliclazide and placebo experiments. It is therefore unlikely that portal concentrations of insulin were different on the two occasions.

Factors other than plasma insulin concentration modulate HGP. An increase in plasma glucose concentration can directly diminish HGP.[20] However, both the absolute value and the increment in plasma glucose level were reduced following gliclazide ingestion, so that a lower suppressive effect by glucose would be expected in those studies. Nevertheless, a potentiating effect of glucose-mediated suppression of HGP might be postulated on the basis of the results of study C. When no glucose increment, actually a decrement, occurs, pharmacologic doses of gliclazide do not appear to exert any effect on the liver. Plasma glucagon accounts for 75% of basal HGP,[21] and a more effective inhibition of its secretion could contribute to reduce postglucose HGP. Such an effect of sulfonylurea agents has been suggested by Fallucca et al.[22] Still, this does not seem to be the case in our study. The plasma glucagon concentration, in fact, was not reduced to a different extent by gliclazide or placebo (Fig 4). Others have proposed that improvement in glucose tolerance after sulfonylurea therapy may depend on a greater suppression of plasma FFA concentration.[23] We have investigated this possibility, but plasma FFA level was not affected by acute administration of gliclazide. The lack of significant changes in plasma FFAs also suggests that no major difference in plasma insulin occurred in the two studies, given the exquisite sensitivity of lipolysis to insulin.[18,20]

To directly assess the effect of short-term administration of gliclazide on glucose metabolism in the presence of comparable portal and peripheral insulin concentrations, an isoglycemic clamp study was performed. Results of this set of studies clearly show that short-term administration of the sulfonylurea does result in a greater suppression of HGP without producing a significant alteration in overall glucose disposal (Fig 5), in agreement with previous analogous studies.[24,25] However, it must be emphasized that this experimental approach also cannot identify whether gliclazide action on the liver is mediated by enhancement of the suppressive effect of HGP by hyperinsulinemia and/or hyperglycemia, since an isoglycemic rather than a euglycemic insulin clamp was used.

Taken together, the results of these two studies provide evidence that the larger inhibition of HGP following glucose infusion and gliclazide ingestion is not mediated by the drug's action on pancreatic hormones or FFA metabolism. It is therefore appropriate to postulate that gliclazide exerts a direct effect on liver glucose metabolism. This view is supported by several in vitro studies[3] reporting increased insulin binding to surface receptors and activation of several enzymatic reactions that may cause reduced HGP.

The second point raised by the present study is that even though gliclazide can exert a specific effect on the liver, it looks like this action requires the presence of insulin or hyperglycemia to be elicited. In fact, when drug or placebo were given along with somatostatin to avoid changes in insulin and glucagon versus baseline levels, a comparable decline in plasma glucose was apparent (Fig 7). Somatostatin infusion may reduce splanchnic blood flow[26] and impair drug absorption from the gut, and therefore decrease plasma gliclazide. Without direct estimation of the plasma level of the drug, this possibility cannot be ruled out. Nevertheless, these in vivo results are strongly in keeping with the in vitro experiences. A significant potentiation of insulin action has been reported in perfused liver preparations, primary hepatocyte cultures, and isolated hepatocytes.[3]

A potentiation of insulin-mediated glucose disposal by peripheral tissues of NIDDM patients has been suggested after prolonged treatment with gliclazide.[24,25,27] In the present study, the rate of glucose utilization was measured by an isotopic technique both in response to IV glucose infusion and during an isoglycemic moderately hyperinsulinemic clamp study. Inspection of Fig 2 shows that overall glucose disposal was not influenced by gliclazide administration. This may be explained by different study protocols: long-term treatment in the former study and short-term in the present study. In fact, it is now accepted that improvements in insulin action can be secondary to a reduction in the overall plasma glucose concentration.[7] As for the glucose clamp study, it should be pointed out that the present experimental approach may not be the more appropriate one to ascertain an effect of sulfonylureas on insulin-mediated glucose metabolism in peripheral tissues. The plasma insulin concentration attained during the clamp study ($\approx$180 pmol/L) barely reaches the threshold for insulin promotion of glucose utilization at the muscle level.[28]

In conclusion, we suggest that gliclazide can exert a specific action on liver glucose metabolism. This effect is synergistic with insulin action and/or concomitant hyperglycemia. As such, it may provide a useful tool for improving the postprandial glucose profile in NIDDM.

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