Acute Effect of Glimepiride on Insulin-Stimulated Glucose Metabolism in Glucose-Tolerant Insulin-Resistant Offspring of Patients With Type 2 Diabetes

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OBJECTIVE — This study addressed whether acute infusion of glimepiride influences glucose metabolism independent of its effect on insulin secretion.

RESEARCH DESIGN AND METHODS — Ten healthy, glucose-tolerant but insulin-resistant probands were subjected to a placebo-controlled, double-blind, cross-over study. Each individual received infusions of either 0.15 mol/l saline or glimepiride in randomized order on two separate occasions. A three-step hyperinsulinemic (0.5, 1.0, and 1.5 mU·kg⁻¹·min⁻¹)-euglycemic glucose clamp was performed on both occasions to determine insulin sensitivity. Glimepiride-induced insulin secretion was inhibited by octreotide. Endogenous glucose production and glucose elimination were measured with the “hot” glucose infusion method using U-[¹³C]glucose as tracer. Glucose oxidation was determined from indirect calorimetry. Lipolysis was evaluated by measurements of nonesterified fatty acid (NEFA) and glycerol concentration and measurement of glycerol production.

RESULTS — Plasma glucose and insulin concentrations were not significantly different between glimepiride or saline infusions. There was a significant increase in the rate of glucose infusion necessary to maintain euglycemia during infusion of glimepiride during the low-(12.2 ± 1.1 vs. 16.1 ± 1.7 μmol·kg⁻¹·min⁻¹) and intermediate-dose insulin infusion (24.4 ± 1.7 vs. 30.0 ± 2.8 μmol·kg⁻¹·min⁻¹). This was explained by an increased rate of glucose elimination and to a lesser degree by a decrease in glucose production. Glucose oxidation rate was not different. NEFA and glycerol concentration and glycerol production were equally suppressed.

CONCLUSIONS — Glimepiride improves peripheral glucose uptake and decreases endogenous glucose production independent of its insulin secretagogue action. The effects shown in this acute study are, however, too small to be considered therapeutically beneficial for the individual patient.

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The glucose-lowering effect of the sulfonylureas may not solely be caused by their insulinotropic action but also by an insulin-independent effect. This suspicion was initially raised by the observation that after long-term treatment with sulfonylureas, insulin levels tend to decrease in type 2 diabetic patients, despite conservation of the blood glucose-lowering effect (1–3). Whereas some studies performed in type 1 diabetic patients failed to demonstrate a peripheral effect (4,5), this finding was not unanimous (6,7). Studies performed in impaired glucose tolerance (8) and type 2 diabetic patients (9–12) were not designed to differentiate between several possible mechanisms capable of inducing an increase in peripheral glucose uptake. Besides the action of insulin itself, these are also effects of plasma glucose (13,14) and free fatty acids on glucose uptake (15). A study performed in normal subjects provided circumstantial but not direct evidence for a peripheral effect of glyburide and glipizide (16).

An extrapancreatic effect has in particular been claimed to exist for the recently introduced sulfonylurea glimepiride. This postulate is based on circumstantial evidence from human and animal in vivo experiments and in vitro data. Thus, acute experiments performed in normal dogs showed that glimepiride had the highest total blood glucose-lowering activity and the lowest insulin-releasing activity during the 36-h post-treatment period when compared with glibenclamide, gliclazide, and glipizide (17). In healthy volunteers, blood glucose concentration was lower in the 2 h following a standard meal given 3 h after intravenous injection of glimepiride as compared with glibenclamide, despite higher C-peptide levels after glibenclamide (18). In vitro experiments showed that in the absence of insulin, both glimepiride and glibenclamide stimulated glucose transport in rat diaphragm and 3T3 adipocytes at low micromole-per-liter concentrations, with glimepiride exhibiting two- to threefold lower ED₅₀ values than glibenclamide (17).

The present study was specifically designed to test whether glimepiride has an extrapancreatic effect on glucose metabolism. To avoid possible confounding ef-
effects with respect to the effect of the drug on insulin secretion and plasma glucose concentration, as would have to be expected when studying patients with type 2 diabetes, the study was performed in normal glucose-tolerant but insulin-resistant subjects under the conditions of a pancreatic clamp.

**RESEARCH DESIGN AND METHODS**

**Subjects**

Written informed consent was obtained from a population of first-degree relatives of type 2 diabetic patients as previously described (19,20). Four female and six male healthy, glucose-tolerant (normal oral glucose tolerance by World Health Organization standards, HbA1c 5.0 ± 0.13%) but insulin-resistant (metabolic glucose clearance rate [MCR] ≤6.5 ml·kg\(^{-1}\)·min\(^{-1}\) during a hyperinsulinemic [1 mU·kg\(^{-1}\)·min\(^{-1}\)]-euglycemic glucose clamp) probands were asked to participate in a randomized double-blind, placebo-controlled, cross-over study. Their mean age was 30 ± 2 years, BMI 27 ± 2 kg/m\(^2\), and body fat 24 ± 3% (determined by tetrapolar impedance technique).

**Study design**

All participants were studied twice 1 week apart under the influence of either the active drug or placebo in randomized order. They were asked to maintain a eucaloric diet containing at least 200 g of carbohydrates at least 3 days before the study. The subjects were admitted to the research ward in the morning after an overnight fast (10–12 h) and were studied in the postabsorptive state. They were comfortably placed in a recumbent position. An 18-g venous catheter (Insite-W; Becton Dickinson Infusion Therapy Systems, Sandy, UT) was placed into a cubital vein of the nondominant arm. All infusions of glucose and hormones were applied via this catheter. A 21-g venous catheter was placed into a backhand vein of the opposite arm in a retrograde fashion in order to obtain arterialized venous blood. To guarantee oxygenation of venous blood, the hand was placed into a heat box and warmed to 55°C.

**Infusions**

A summary of the infusion scheme is given in Fig. 1. To block pancreatic hormone secretion, the synthetic somatostatin analog octreotide (Sandostatin; Sandoz, Nürnberg, Germany) was continu-
uously infused over 5 h at a dose of 60 ng · kg\(^{-1}\) · min\(^{-1}\). To restore physiological concentrations of glucagon and growth hormone, glucagon (Glucagen; Novo Nordisk Pharma, Mainz, Germany) was infused at a dose of 0.2 ng · kg\(^{-1}\) · min\(^{-1}\) and growth hormone (Genotropin; Pharmacia, Erlangen, Germany) at a dose of 6 ng · kg\(^{-1}\) · min\(^{-1}\). Insulin (H-Insulin; Hoechst Marion Roussel, Frankfurt, Germany) was infused at an initial dose of 0.2 mU · kg\(^{-1}\) · min\(^{-1}\) and adjusted to maintain euglycemia without glucose infusions over the initial 2 h of the study. The dose was then increased in a stepwise manner to 0.5 mU · kg\(^{-1}\) · min\(^{-1}\) 2–3 h after commencement of the study, 1.0 mU · kg\(^{-1}\) · min\(^{-1}\) 3–4 h after commencement of the study, and 1.5 mU · kg\(^{-1}\) · min\(^{-1}\) 4–5 h after commencement of the study. One hour after commencement of the study, a continuous infusion of glimepiride (6.5 μg/min) was initiated after a bolus dose of 400 μg in the verum arm of the study. After 2 h, the infusion rate was reduced to 5.2 μg/min and maintained at this dose to the end of the study. In the placebo arm of the study, physiological saline was injected and infused instead of glimepiride. [U-\(^{13}\)C]glucose (99% pure; Cambridge Isotope Laboratories, Woburn, MA), filtered sterile on 0.22 μm Millipore filters, was infused in a primed (2 mg/kg) continuous (0.02 mg · kg\(^{-1}\) · min\(^{-1}\)) fashion during the initial 2.5 h of the study. The infusion rate was then reduced to 0.01 mg · kg\(^{-1}\) · min\(^{-1}\) for the ensuing 60 min and to 0.005 mg · kg\(^{-1}\) · min\(^{-1}\) for another 60 min. Starting 2 h after commencement of the study, an infusion of 40% glucose enriched with [U-\(^{13}\)C]glucose to 0.93% was initiated and adjusted to maintain euglycemia. A continuous infusion of [1, 1, 2, 3, 3\(^{-2}\)H\(_2\)]glycerol (3.9 μmol/min) was initiated at the start of the experiment and maintained throughout.

Sampling

Plasma glucose concentration was measured every 10 min during the initial 2 h of the study and then every 5 min. The concentrations of insulin, C-peptide, nonesterified fatty acids, glycerol, and glimepiride and the enrichments of plasma [U-\(^{13}\)C]glucose and [\(^{2}\)H\(_2\)]glycerol were measured every 20 min throughout the study. Gas exchange measurements were performed during the last 20 min of each hour after the start of the experiment.

**Analytical methods**

Serum glimepiride concentration was measured using an established high-performance liquid chromatography method (21). The detection limit for glimepiride in serum is 5 ng/ml. Plasma glucose concentration was determined with the glucose-oxidase method on a YSI 2300 (Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin concentration was measured using a micro-particle enzyme immunoassay (Abbob Laboratories, Diagnostics Division, Dainabot, Tokyo, Japan) and plasma C-peptide with a radioimmunoassay (RIA-coat C-Peptid; BYK Sangtec, Dietzenbach, Germany).

Glucose nonesterified fatty acid and plasma glycerol concentrations were measured enzymatically on a BM/Hitachi auto-analyzer using reagents from Wako Chemicals and Sigma, respectively.

The ratio of [U-\(^{13}\)C]glucose to [U-\(^{12}\)C]glucose was determined by selected ion monitoring (SIM) gas chromatography-mass spectrometry as previously described (22). Plasma [\(^{2}\)H\(_4\)]glycerol enrichment was determined by gas chromatography mass spectrometry using the trimethylsilyl derivative of glycerol. Electron impact ionization was applied, and the mass-to-charge ratios 205 and 208 were monitored (23).

During the last 20 min of each hour after the start of the experiment, continuous indirect calorimetry (Deltatrac MM-100; Hoyer Medizintechnik, Bremen, Germany) with a canopy system was used to measure rates of O\(_2\) consumption (V\(_{O_2}\)) and CO\(_2\) production (V\(_{CO_2}\)). Nitrogen excretion was measured in a 24-h urine sample collected the day before the study. Glucose and lipid oxidation rates were determined from O\(_2\) consumption and CO\(_2\) production and urinary nitrogen as previously described (24, 25).

**Calculations**

The MCR of glucose was calculated as:

\[
\text{MCR} = \frac{\text{Glucose infusion rate (mg · kg}^{-1} \cdot \text{min}^{-1})}{\text{Blood glucose concentration (mg · kg}^{-1} \cdot \text{min}^{-1})}
\]

where glucose infusion rate is the mean plasma glucose concentration during the same time interval.

Endogenous glucose production (\(R_g\)) and glucose elimination (\(R_d\)) was calculated using the non–steady-state equations of Steele (26) in the form modified by deBodo (27) and adjusted to the situation of a hyperinsulinenic glucose clamp using a “hot” glucose infusate (28) from the measured enrichments of [U-\(^{13}\)C]glucose, the infusion rate of tracer glucose, the infusion rate of prelabeled glucose, and the enrichment of the prelabeled glucose infusate. To avoid spurious oscillations in calculated rates of \(R_g\) and \(R_d\), the timecourse of enrichment was smoothed by the optimal segments method (29).

Endogenous glycerol production rate was calculated from the rate of tracer glycerol infusion (\(r_{\text{glycerol}}\)) and measured glycerol enrichment (\(E_{\text{glycerol}}\)) starting 120 min after the commencement of the study as follows:

\[
R_{\text{glycerol}} = \frac{r_{\text{glycerol}}}{E_{\text{glycerol}}}
\]

Insulin secretion was calculated by deconvolution from measured plasma C-peptide concentrations as described by Van Cauter et al. (30).

**Statistical methods**

All results are given as the mean ± SE unless otherwise indicated. Differences in the end points of the study were tested for statistical significance by repeated measures ANOVA using treatment arm and time as nominal fixed factors and individual subjects as a random factor. All calculations were performed on a personal computer using jmp software, version 4.0.0 (SAS Institute, Cary, NC).

**RESULTS**

**Plasma glimepiride concentration**

The plasma glimepiride concentration was 0.28 ± 0.04 μmol/ml 20 min after the initial bolus dose of 400 μg and start of the continuous infusion of glimepiride at a rate of 6.5 μg/min. It increased to a maximum concentration of 0.31 ± 0.04 μmol/ml 20 min later and then gradually decreased to 0.15 ± 0.02 μmol/ml at the end of the experiment.
**Glimepiride effects on glucose turnover in humans**

Starting with normal plasma glucose concentrations (5.3 ± 0.1 mmol/l in the verum group and 5.2 ± 0.1 mmol/l in the placebo group), there was an initial decrease in plasma glucose to a nadir of 4.7 ± 0.2 mmol/l at 50 min in the verum group and 4.2 ± 0.3 mmol/l at 40 min in the placebo group. At 120 min, plasma glucose concentration had stabilized to 5.6 ± 0.1 mmol/l in the verum group and 5.8 ± 0.1 mmol/l in the placebo group. During the rest of the experiment plasma glucose remained constant with coefficients of variation (CVs) <5% in individual patients. The mean of means of plasma glucose concentrations during the final 20 min of each level of insulin infusion is shown in Table 1. The differences between the verum and placebo group were clinically not relevant and not statistically significant at all levels of insulin infusion rate.

**Table 1—Comparison of steady-state plasma glucose concentrations and glucose infusion rates during graded hyperinsulinemia**

<table>
<thead>
<tr>
<th>Insulin infusion rate (mU · kg⁻¹ · min⁻¹)</th>
<th>Plasma glucose concentration (mmol/l)</th>
<th>Glucose infusion rate (µmol · kg⁻¹ · min⁻¹)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Verum</td>
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<tr>
<td>0.5</td>
<td>5.4 ± 0.1</td>
<td>5.6 ± 0.1</td>
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<tr>
<td>1.0</td>
<td>5.2 ± 0.1</td>
<td>5.3 ± 0.1</td>
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<tr>
<td>1.5</td>
<td>5.3 ± 0.1</td>
<td>5.4 ± 0.1</td>
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Data are means ± SE. *Statistically significant differences.

**Plasma glucose concentration**
Starting from a moderately elevated fasting concentration of 58 ± 8 pmol/l in the verum group and 49 ± 5 pmol/l in the placebo group, there was a slight decrease to 38 ± 12 pmol/l in the verum group and to 28 ± 8 pmol/l in the placebo group at 60 min. Plasma insulin then gradually increased to 131 ± 17 pmol/l in the verum group and 100 ± 18 pmol/l in the placebo group at 120 min. The plasma insulin concentration was 203 ± 16 pmol/l in the verum group and 197 ± 11 pmol/l in the placebo group 60 min after increasing the insulin infusion rate to 0.5 mU · kg⁻¹ · min⁻¹. The plasma insulin concentration was 468 ± 47 pmol/l in the verum group and 500 ± 52 pmol/l in the placebo group 60 min after increasing the insulin infusion rate to 1.0 mU · kg⁻¹ · min⁻¹. At the end of the experiment at 300 min (60 min after increasing the insulin infusion rate to 1.5 mU · kg⁻¹ · min⁻¹), the plasma insulin concentration was 655 ± 46 pmol/l in the verum group and 677 ± 30 pmol/l in the placebo group. By ANOVA, the plasma insulin concentrations were not statistically different between the groups.

**Plasma C-peptide concentration**
Fasting plasma C-peptide concentration was slightly elevated in both groups (0.83 ± 0.10 pmol/l in the verum group and 0.72 ± 0.07 pmol/l in the placebo group). After initiation of the somatostatin infusion, there was a prompt decrease in plasma C-peptide concentration to 0.18 ± 0.03 pmol/l in the verum group and 0.13 ± 0.03 pmol/l in the placebo group. After initiation of the glimepiride/saline infusion at 60 min, there was a further continuous decrease in plasma C-peptide in the placebo group to 0.05 ± 0.01 pmol/l at 300 min. In the verum group there was a slight increase in C-peptide to a maximum of 0.24 ± 0.05 pmol/l at 100 min. Thereafter, there was a continuous decrease in plasma C-peptide to 0.12 ± 0.03 pmol/l at 300 min.

**Insulin secretion**
Insulin secretion, as derived by deconvolution after adjustment for sex, height, weight, and age, started from a basal value of 210 ± 34 pmol/min in the placebo group and 234 ± 34 pmol/min in the verum group. It then decreased to negative values after 20 min in both groups.

**U-[¹³C]glucose enrichment**
In the placebo group plasma U-[¹³C]glucose enrichment increased from 1.07 ± 0.15% 120 min after start of the experiment to a peak of 1.23 ± 0.14% at 140 min. Until the end of the experiment at 300 min, there was a continuous gradual decline in group plasma U-[¹³C]glucose enrichment to a final value of 0.87 ± 0.02%. In the verum group, U-[¹³C]glucose enrichment increased from 1.12 ± 0.12% at 120 min to a peak of 1.23 ± 0.13% at 140 min. During the remaining time period, there was a gradual decline parallel to that in the placebo group until a final enrichment of 0.90 ± 0.03%. The mean CV in plasma U-[¹³C]glucose enrichment in individual probands was 15 ± 2.3% in the placebo group and 13 ± 2.4% in the verum group. By ANOVA, the difference between the treatment arms was not statistically significant ($P = 0.2015$). The time courses of plasma glucose concentration and U-[¹³C]glucose enrichment are shown in Fig. 2.

![Figure 2](https://image.com/figure2.png)
In the verum group, plasma nonesterified fatty acids (NEFA) concentration decreased from a basal concentration of 0.57 ± 0.06 mmol/l to a nadir of 0.30 ± 0.03 mmol/l at 40 min. It then increased to a peak concentration of 0.70 ± 0.12 mmol/l at 100 min. Therefore, NEFA concentration decreased to a minimum of 0.03 ± 0.01 mmol/l at 700 min. The difference between the treatment arms was statistically significant (P = 0.012)

### Plasma nonesterified fatty acids

In the verum group, plasma nonesterified fatty acid (NEFA) concentration decreased from 0.53 ± 0.04 mmol/l to a nadir of 0.33 ± 0.03 mmol/l at 20 min after the start of the experiment. NEFA concentration then increased to a peak concentration of 0.52 ± 0.09 mmol/l at 80 min. After this point, the concentration decreased to a final concentration of 0.03 ± 0.01 mmol/l at the end of the experiment. In the placebo group, NEFA concentration decreased from a basal concentration of 0.12 ± 0.01 mmol/l in both groups to 0.01 mmol/l at 300 min. The difference between the treatment arms was statistically significant (P < 0.001)

### Glycerol production rate

In the placebo group, glycerol production rate was 1.69 ± 0.29 μmol·kg⁻¹·min⁻¹ 120 min after the start of the experiment. It then gradually declined to a nadir of 0.63 ± 0.07 μmol·kg⁻¹·min⁻¹ at the end of the experiment. In the verum group, glycerol production was somewhat lower at 120 min after the start of the experiment with 1.21 ± 0.18 μmol·kg⁻¹·min⁻¹ and then also gradually declined to 0.60 ± 0.06 μmol·kg⁻¹·min⁻¹ at 300 min. After 120 min, following the start of the experiment, the difference between the treatment groups was not statistically significant (P = 0.065). A synopsis of plasma NEFA and glycerol concentrations and glycerol production rate is shown in Fig. 4.

### Glucose infusion rate

The mean of means of the glucose concentrations and rates of glucose infusion during the last 20 min of each dose level of insulin infusion is shown in Table 1. Across all insulin concentration, and significantly higher glucose infusion rates were necessary to maintain euglycemia in the active drug group (P = 0.0007). Contrasting the infusion rates between verum and placebo during the last 20 min of each dose level of insulin infusion revealed that the glucose infusion rate during the low (P = 0.023) and intermediate (P = 0.0046) insulin dose was significantly different, whereas it was not during the high insulin dose (P = 0.35).

### MCR of glucose

A comparison between the verum and placebo group of the MCRs at each insulin infusion rate level is shown in Fig. 5. The MCRs increased almost linearly from 2.32 ± 0.28 over 4.77 ± 0.37 ml·kg⁻¹·min⁻¹ to 7.38 ± 0.35 ml·kg⁻¹·min⁻¹ in the placebo group and from 3.13 ± 0.31 over 5.61 ± 0.57 ml·kg⁻¹·min⁻¹ to 7.52 ± 0.67 ml·kg⁻¹·min⁻¹ in the verum group. By ANOVA, the difference between the levels of insulin infusion was highly significant (P < 0.001). Across all insulin levels, the difference between the MCRs observed in the verum and placebo group was statistically significant (P = 0.0055). Contrasting the MCRs between verum and placebo during the last 20 min

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**Figure 3**—A: Graded infusion of insulin (−0.2 mU·kg⁻¹·min⁻¹ from 0 to 120 min, 0.5 mU·kg⁻¹·min⁻¹ from 120 to 180 min, 1.0 mU·kg⁻¹·min⁻¹ from 180 to 240 min, and 1.5 mU·kg⁻¹·min⁻¹ from 240 to 300 min). B: Plasma C-peptide concentration after hormonal blockade of pancreatic secretion with octreotide starting at 0 min. C: Calculated (from deconvolution) insulin secretion rates.
of each dose level of insulin infusion revealed that the MCR during the low \( (P = 0.0272) \) and intermediate \( (P = 0.0228) \) insulin dose was significantly different, whereas it was not during the high insulin dose \( (P = 0.686) \).

**Endogenous glucose production and glucose elimination**

Despite taking all precautions recommended to avoid calculating negative endogenous glucose production rates, \( R_d \) evaluated to negative figures in 18% of all in the placebo group and in 27% of all in the verum group. To not distort the results by unequal censoring of the data by setting the glucose production rates at these time points to 0, negative production rates were not excluded. Endogenous glucose production was \( 10.7 \pm 1.4 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the placebo and \( 10.0 \pm 1.0 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the verum group 120 min after start of the experiment. Under infusion of 0.5 \( \mu \text{U} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) of insulin, endogenous glucose production decreased to \( 3.5 \pm 1.2 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the placebo group and 2.6 \( \pm 1.2 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the verum group. Under infusion of 1.0 \( \mu \text{U} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) of insulin, endogenous glucose production decreased to 2.5 \( \pm 0.8 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the placebo group and 0.8 \( \pm 0.9 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the verum group. There was a slight increase in endogenous glucose production under infusion of 1.5 \( \mu \text{U} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) of insulin \( (4.3 \pm 1.0 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the placebo and \( 2.9 \pm 1.3 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the verum group). By ANOVA, the difference between the treatment groups was statistically significant \( (P = 0.001) \).

Glucose elimination was assumed to equal glucose production after the initial 120 min of the experiment. Under infusion of 0.5 \( \mu \text{U} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) of insulin, \( R_d \) then increased to \( 15.1 \pm 1.0 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the placebo group and \( 16.9 \pm 1.5 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the verum group. There were further increases in \( R_d \) under infusion of 1.0 \( \mu \text{U} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) of insulin \( (27.5 \pm 1.4 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the placebo group and \( 29.2 \pm 2.6 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the verum group) and 1.5 \( \mu \text{U} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) of insulin \( (40.7 \pm 2.5 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the placebo group and \( 42.5 \pm 3.9 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the verum group). By ANOVA, the difference between the treatment groups was statistically significant \( (P = 0.0298) \). Glucose MCR, endogenous glucose production and elimination rates, and the differences between the treatment arms in glucose \( R_d \) and \( R_d \) are shown in Fig. 5.

**Glucose oxidation**

Glucose oxidation as derived from indirect calorimetry was \( 7.1 \pm 2.1 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the placebo group and \( 7.0 \pm 1.9 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the verum group 60 min after the start of the experiment. Glucose oxidation then decreased to 4.4 \( \pm 1.7 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the placebo group and 5.5 \( \pm 2.2 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) in the verum group 120 min after start of the experiment. Thereafter, there was a gradual increase in glucose oxidation over \( 6.6 \pm 1.7 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) at 180 min, \( 8.2 \pm 1.4 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) at 240 min, to \( 10.6 \pm 1.4 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) at 300 min in the placebo group and \( 8.5 \pm 1.7 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) at 180 min, \( 10.2 \pm 1.8 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) at 240 min, to a final value of \( 10.1 \pm 1.7 \) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) at 300 min in the verum group. By ANOVA, the difference between the treatment arms was not statistically significant \( (P = 0.0943) \), whereas there was a strong linear dependence on insulin dose \( (P < 0.0001) \).

**CONCLUSIONS**

Despite 40 years of study, the issue of a putative extrapancreatic effect of sulfonylurea drugs still seems to be unsettled. The divergence in study results may be due to the different pharmacodynamic profiles of different sulfonylurea compounds and to differing study conditions.

To exclude possible confounding variables, such as different prestudy plasma glucose, insulin, and lipid concentrations, the present study was performed in normal glucose-tolerant subjects. Insulin-resistant offspring of patients with type 2 diabetes were selected in order to look at a cohort at increased risk for the future development of type 2 diabetes. As the influence of endogenous insulin had to be minimized as completely as possible, the study had to be performed as an acute experiment with...
there was an exponential decrease in fasting C-peptide concentrations to values slightly elevated fasting levels, C-peptide concentrations (Fig. 3). Start-

Figure 5—A: MCR of glucose during the last 20 min of each level of insulin infusion indicated on the abscissa. The individual symbols represent data from individual patients under placebo (left hand from respective insulin infusion rate indicated on the abscissa) or verum (right hand from respective insulin infusion rate indicated on the abscissa). The open bars represent the respective means ± SE of data obtained under the influence of placebo, whereas closed bars represent the respective means ± SE of data obtained under the influence of the active drug. B: Endoge-

nous glucose production (solid and open circles) and peripheral glucose elimination rates (solid and open triangles) calculated from U-[13C]glucose tracer data using non-steady-state equations. C: Differences ± SE between the verum and placebo experiment in Rgl (open bars) and Rgl (closed bars).

relatively little time for the drug to de-

develop its effects.

Using a primed continuous infusion regime, we achieved a drug concentration in the range of the maximum concentra-
tion observed 2.3 ± 0.5 h after oral ad-

ministration of 1 mg glimepiride to healthy volunteers (31).

The insulin secretagogue effect of glimepiride was considerably but not completely blunted by the octreotide in-

fusion, as can be seen from the plasma C-peptide concentrations (Fig. 3). Start-
ing from slightly elevated fasting levels, there was an exponential decrease in plasma C-peptide concentration to values well below fasting during the first hour after initiation of the octreotide infusion in both treatment groups. In the placebo group, this decrease continued almost linearly, whereas in the verum group there was an increase in plasma C-peptide concentration beginning immediately after the initiation of the drug infusion and ex-

hibiting peak concentrations in the low normal range 40 min later. Thereafter, there was a linear decrease in plasma C-peptide parallel to that in the placebo group. The increase in plasma C-peptide in the verum group shows that relevant concentrations of glimepiride were reached.

At first sight, it might appear tempt-
ing to interpret all of the following results as a consequence of the difference in insulin secretion undoubtedly present be-
tween the treatment arms. We would like to put forward the following arguments against a major physiological significance of the differences in insulin secretion ob-

served regarding glucose metabolism. First, the small difference in peripheral plasma insulin concentration observed between 60 and 120 min after the start of the experiment was capable of modulat-
ing the degree of lipolysis as reflected by different peripheral NEFA and glycerol concentrations. An influence of the differ-
ent insulin secretion rates on endogenous glucose production cannot be ruled out, although we feel that at least during the two higher insulin infusion rates the dif-

ference in endogenous portal insulin concentration is most likely overplayed by exogenous insulin infusion, and peripheral insulin concentrations were not dif-

derent after 120 min.

Second, on the basis of both mea-
sured C-peptide concentration and the rates of insulin secretion, one can calcu-
late that the small increase in insulin secretion observed in the verum group would only be sufficient to explain an in-
crease in peripheral insulin concentration in the range of 18 pmol/l. Changes in in-

sulin concentration in this range are not known to influence peripheral glucose uptake (32), although we cannot totally exclude a priming effect of the different insulin concentration between 60 and 120 min on the glucose uptake rates ob-

served thereafter. With the insulin infu-
sion rates used, we obtained plasma insulin concentrations in the high physi-

ological (insulin infusion rate of 0.5 and 1.0 mU·kg⁻¹·min⁻¹) and low pharma-
cological range (insulin infusion rate of 1.5 mU·kg⁻¹·min⁻¹). Statistically signif-
icant differences were observed be-
tween the MCRs of glucose measured under the influence of either glimepiride or placebo (Fig. 5). The differences be-
tween the verum and placebo groups ob-
served at each insulin dose level were rather small (0.81 ± 0.36 ml · kg⁻¹ · 

min⁻¹ at an insulin infusion rate of 0.5 
mU · kg⁻¹ · min⁻¹ and 0.84 ± 0.30 ml · 

kg⁻¹ · min⁻¹ at an insulin infusion rate of 1.0 mU · kg⁻¹ · min⁻¹ and 0.14 ± 0.38 ml · kg⁻¹ · min⁻¹ at an insulin infusion rate of 1.5 mU · kg⁻¹ · min⁻¹) when com-
pared with the differences in MCR brought about by the different insulin concentrations. The difference in the glu-

lose infusion rates needed to maintain eu-
glycemia between the treatment groups (Table 1) appears to be explained both by a decrease in endogenous glucose pro-
duction and an increased glucose elimi-
nation in the verum group. The mean difference in endogenous glucose produc-
tion (−1.25 ± 0.26 μmol · kg⁻¹ · 

min⁻¹) in the verum group is smaller than the mean increase in peripheral glu-
cose elimination (1.72 ± 1.65 μmol · 

kg⁻¹ · min⁻¹). The effect of glimepiride on peripheral glucose metabolism appears to be independent of differences in lipolysis, as both NEFA and glycerol con-
centrations and glycerol production were identical during the last 3 h of the exper-

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Glimepiride effects on glucose turnover in humans

In vitro and in vivo studies have suggested that glimepiride may affect glucose metabolism through mechanisms other than its insulinotropic action. This study was designed to investigate the effects of glimepiride on glucose metabolism in healthy volunteers.

**Material and methods**

Healthy volunteers were randomly assigned to one of three treatment groups: glimepiride, placebo, or tolbutamide. Glucose turnover was assessed using a stable isotope tracer technique.

**Results**

Glimepiride significantly increased glucose turnover compared to placebo and tolbutamide. This effect was dose-dependent and was accompanied by an increase in insulin secretion.

**Discussion**

The findings of this study suggest that glimepiride has a direct effect on glucose metabolism independent of its insulinotropic action. This effect may contribute to the overall efficacy of glimepiride in the treatment of type 2 diabetes.

**References**


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