Assessment of insulin action in man: role of hyperglycemia

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Abstract. The effect of hyperglycemia on insulin-induced glucose metabolism (M) was investigated in healthy subjects using sequential clamp protocols at constant insulin + somatostatin infusions and varying plasma glucose. During euglycemia (4.8 mmol/l) M increased from 5.6 to 12.5 mg·kg⁻¹·min⁻¹ with increasing plasma insulin (0.54–3.00 nmol/l). At increasing glucose (6.7 mmol/l), M further increased (9.7 to 19.2 mg·kg⁻¹·min⁻¹) with the plasma insulin level (0.41 to 2.99 nmol/l). At a plasma glucose level of 9.8 mmol/l insulin (0.42 to 3.17 nmol/l) was still effective to increase M (13.7 to 25.2 mg·kg⁻¹·min⁻¹). Regression analysis showed that hyperglycemia does not only increase the maximal insulin-stimulated M, but also decreases the insulin concentration causing a half maximum effect. During prolonged clamp studies M increased by about 10% per h, independent by the plasma glucose level. We conclude that hyperglycemia increases M by increasing insulin responsiveness as well as insulin sensitivity. Data derived from euglycemic clamp studies alone are of limited value with respect to the assessment of insulin action.

Impaired glucose tolerance, noninsulin-dependent diabetes mellitus, and obesity are associated with insulin resistance. Various methods are used to assess insulin action 'in vivo', e.g. oral/intravenous glucose tolerance tests, forearm perfusion/hepatic venous catheterization, glucose clamp studies or infusions of glucose-insulin together with somatostatin, epinephrine and propranolol (Bergman et al. 1985). Today the glucose clamp technique provides the most accurate determination of insulin action in man. The method is based on the measurement of the amount of glucose that must be infused to maintain plasma glucose levels during a period of hypersulinemia. This technique determines insulin's ability to inhibit endogenous glucose production as well as to promote glucose disposal during constant insulin infusion under steady state conditions.

The glucose clamp technique was first introduced by DeFronzo et al. (1979). Since then a variety of protocols have been used differing with respect to the glucose levels aimed at or to the insulin infusion rate. Using a sequential clamp protocol, insulin infusions can be given at different rates while maintaining euglycemia (Rizza et al. 1981). If insulin then is plotted versus the clamp-derived glucose disposal rate (M), this results in a typical sigmoid shaped dose-response curve suggesting that M is a function of the plasma insulin level. This is also seen during a hyperglycemic clamp protocol (Gottesman et al. 1984). However, increasing the plasma glucose level at a constant insulin infusion rate increases M too, providing evidence that both insulin and glucose increase glucose utilization (Gottesman et al. 1984; Yki-Järvinen et al. 1987). This finding is of particular interest for clamp studies, if one compares insulin sensitivity of individuals differing with respect to their basal plasma glucose concentrations. Furthermore, euglycemic clamp data alone may be misleading if one considers physiological conditions during meals, where both plasma insulin and glucose concentrations in-
crease and stimulate glucose utilization. Since glucose per se inhibits endogenous glucose production (Müller et al. 1988a, this may also influence the assessment of insulin action at different plasma glucose levels. To get further insight into the interaction of insulin and glucose regulating glucose metabolism, the present study was performed using sequential clamp protocols at constant insulin infusion rates and varying plasma glucose levels in healthy volunteers. On the basis of our results we wanted to define a better clamp protocol for the assessment of insulin action in clinical studies.

Materials and Methods

Subjects

Experiments were performed in a total of 32 normal lean male subjects (Table 1) in the Metabolic Unit of the Medizinische Hochschule Hannover. All subjects were in good health, none was taking any medication and none had a history of diabetes mellitus or other endocrine diseases. Each subject was informed of the nature, purpose and possible risks of the study and gave his written consent. The study protocol was approved by the Ethical Committee for Human Investigation of the Medizinische Hochschule Hannover.

Experimental protocol

All studies were performed in the postabsorptive state. The subjects were admitted to the hospital at 06.00 h and cannulations were performed: a polyethylene catheter was introduced into the superior vena cava via an antecubital vein for the infusion of all test substances. Intermittent probe sampling was performed in the opposite arm via a second catheter placed retrogradely in a dorsal hand vein for blood withdrawal. This hand was kept in a heating box at 65°C to assure arterIALIZation of venous blood. The baseline protocol started 30 to 60 min after catheterization. Three different types of studies were performed.

Study 1. This study was performed in a total of 21 volunteers and hyperinsulinemic clamps were done for 6 h, at constant insulin infusion rates (3.3, 6.6, 13.3 and 27.0 pmol·kg⁻¹·min⁻¹). Human insulin Hoechst, Frankfurt, FRG) and sequentially increasing plasma glucose levels (0–2 h at euglycemia; 2–4 h at 6.5 mmol/l; 4–6 h at 9.5 mmol/l). To prevent hyperglycemia-induced endogenous insulin secretion, somatostatin (250 µg/h, Stilamin, Serono, Freiburg, FRG) was infused from 0–6 h.

Study 2. Since endogenous glucose production may not be fully suppressed at euglycemia and low insulin infusion rates, hepatic glucose output was assessed in a separate experiment using an euglycemic clamp protocol at different insulin infusion rates (0–2 h: 3.33 pmol·kg⁻¹·min⁻¹ and 2–4 h: 6.66 pmol·kg⁻¹·min⁻¹). In this experiment [³H(3)]glucose (New England Nuclear, Dreieich, FRG) was given as a primed (20 µCi)/constant (0.20 µCi/min) infusion. The clamp protocol was started after an equilibration period of 120 min. Estimation of endogenous glucose production by kinetic analysis of tracer glucose is not feasible, because any application of radioactive substances to healthy subjects is legally forbidden in FRG. Thus, only a single experiment was performed in one of the authors.

Study 3. Since insulin sensitivity increases with time under euglycemic conditions (Doberne et al. 1981), this will affect the data during a prolonged clamp study. Therefore, euglycemic (Study 3A, N = 5) and hyperglycemic clamp studies (aiming at glucose: 9.5 mmol/l;
Study 3B, N = 5) were performed for 4 h at a constant insulin (6.66 pmol·kg⁻¹·min⁻¹) + somatostatin (250 μg/h) infusion.

**Experimental procedures**

Insulin, somatostatin, and glucose (20 and 40% solutions) were given via different peristaltic pumps (Infusomat II, Braun Melsungen, FRG). The infusates were freshly prepared before the experiments, and human serum albumin (2.5 g/l) was added to the solutions to prevent adherence to glassware and tubing. To prevent hypokalemia, potassium chloride was infused together with glucose, its maximum infusion rate did not exceed 20 mmol/h. Clamp studies were performed as described previously (Müller et al. 1986). Plasma glucose was determined every 5 min and appropriate adjustment of the glucose levels was based on an empirical negative feedback algorithm. Plasma insulin and C-peptide were determined at ~20 min and from time 0 up to the end of the protocols at 30-min intervals. Glucose kinetic data were determined as described previously (Müller et al. 1983, 1984).

**Analytical methods**

Plasma glucose was determined by the glucose oxidase method (Glukostat, Beckman Instruments), labelled glucose according to Somogyi’s procedure (Müller et al. 1983, 1984). Plasma insulin and C-peptide concentrations were determined as described in a previous paper (Müller et al. 1986).

**Calculation procedures**

Body mass index (BMI) was calculated according to weight (kg)/height²(m²). The glucose disposal rates (M) was calculated from the glucose infusion rate after correction for deviation in glucose concentrations and urinary glucose losses (DeFronzo et al. 1979; Bratusch-Marrack 1984). M-values were calculated for 20-min intervals; data are given as means of the final 60 min of the different periods of the protocols. The metabolic clearance rate (MCR) for glucose was calculated by dividing M by the plasma glucose concentration and the insulin sensitivity index according to Bergman et al. (1985). Glucose turnover data were assessed from the specific activities of glucose as given in Müller et al. (1984). The MCR for insulin was calculated from the insulin infusion rates and the increment in the plasma insulin levels. The Kₘ-values were obtained from Lineweaver Burke analyses (Fig. 3).

**Presentation of data and statistics**

All data were given as means ± SD. All statistical calculations were performed using standard programmes; analysis for statistical significance was done using ANOVA corrected for repeated measurements, the Wilcoxon signed rank test for paired data, and, if appropriate, Student’s unpaired t-test.

**Study 1**

Baseline plasma glucose, insulin and C-peptide concentrations were comparable in the 4 groups studied (Table 2). Over the range of plasma glucose each increment in glucose resulted in an increase in the glucose disposal rate independently of the insulin infusion rate (Fig. 1, Table 2), but no significant alterations in the MCR for insulin were observed (data not shown). The increase in M per mg of plasma glucose (i.e. ΔM/Δplasma glucose) differed between the different studies (Study 1A: 12.8 (4.9 vs 6.7 mmol/l) and 6.5 (6.7 vs 10.0 mmol/l); Study 1B: 17.0 (4.4 vs 6.6 mmol/l) and 10.5 (6.6 vs 9.5 mmol/l); Study 1C: 16.5 (4.8 vs 6.8 mmol/l) and 10.1 (6.8 vs 10.0 mmol/l); Study 1D: 20.3 (4.9 vs 6.7 mmol/l) and 11.3 (6.7 vs 9.6 mmol/l); all data in ml·kg⁻¹·min⁻¹). The mean increase in M was less between 6.5 and 9.5 mmol/l when compared with the data observed between 4.5 and 6.5 mmol/l. This phenomenon was independent of the plasma insulin level. The disproportionate increase in M was obvious after calculation of M at higher glucose levels according to $M_2 = \frac{g_2}{g_1} \times M_1$ where $M_1$ is the glucose disposal rate at euglycemia, $M_2$ the glucose disposal rate at hyperglycemia, and $g_2$ and $g_1$ are the corresponding plasma glucose concentrations. This calculation yielded 7.6 and 11.5 in Study 1A (6.7 vs 10.0 mmol/l), 10.8 and 15.5 in Study 1B (6.6 vs 9.5 mmol/l), 14.3 and 21.0 in Study 1C (6.8 vs 10.0 mmol/l) and 17.1 and 24.5 in Study 1D (6.7 vs 7.6 mmol/l) (all data in mg·kg⁻¹·min⁻¹). The MCR for glucose was not a glucose-independent measure of insulin action (data not shown). By contrast, the insulin sensitivity index was relatively constant during our experimental conditions.

M increased with increasing plasma insulin levels at every plasma glucose level studied (Table 2, Fig. 2). These increases were linear up to a plasma insulin level of about 1.3 nmol/l but showed non-linearity at an insulin infusion rate of 27 pmol·kg⁻¹·min⁻¹ (Fig 2). Linear regression analysis of the individual data as well as of the reciprocals of M vs plasma insulin (Lineweaver Burke transformation) showed well fitted straight lines at each plasma glucose level (Fig. 3). Increasing plasma glucose does not only increase the maximal response (12.4 vs 26.4 mg·kg⁻¹·min⁻¹ at 4.7 and 9.7 mmol/l, respectively), but also decreased the $K_m$ (i.e. the insulin concentration causing a half maximum effect = 0.45 vs 0.29 mmol/l (Fig. 3).
Fig. 1.
Plasma glucose, plasma insulin, as well as the glucose infusion rate during Study 1A–D.
For number of subjects see Table 1.
An increased insulin sensitivity during the hyperglycemic clamps was also supported by the increase in M per nmol/l insulin at different plasma glucose levels: 4.1 (Study 1B vs 1A), 3.0 (Study 1G vs 1A), and 1.8 (Study 1D vs 1A) at 4.5 mmol/l; 14.1 (Study 1B vs 1A), 3.9 (Study 1C vs 1A) and 2.4 (Study 1D vs 1A) at 6.5 mmol/l, and 18.1 (Study 1B vs 1A), 5.7 (Study 1C vs 1A) and 2.8 (Study 1D vs 1A) at 9.5 mmol/l (Table 2).

Table 2.
Role of hyperglycemia in insulin-induced glucose disposal rate at different insulin infusion rates.

<table>
<thead>
<tr>
<th>Study</th>
<th>Data from study 1, clamp data at aimed glucose concentration</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
</tr>
<tr>
<td>Study A</td>
<td>Glucose, mmol/l</td>
</tr>
<tr>
<td></td>
<td>cv glucose, %</td>
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<tr>
<td></td>
<td>Insulin, nmol/l</td>
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<tr>
<td></td>
<td>C-peptide, nmol/l</td>
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<tr>
<td></td>
<td>M, mg·kg⁻¹·min⁻¹</td>
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<tr>
<td>Study B</td>
<td>Glucose, mmol/l</td>
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<tr>
<td></td>
<td>cv glucose, %</td>
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<tr>
<td></td>
<td>Insulin, nmol/l</td>
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<tr>
<td></td>
<td>C-peptide, nmol/l</td>
</tr>
<tr>
<td></td>
<td>M, mg·kg⁻¹·min⁻¹</td>
</tr>
<tr>
<td>Study C</td>
<td>Glucose, mmol/l</td>
</tr>
<tr>
<td></td>
<td>cv glucose, %</td>
</tr>
<tr>
<td></td>
<td>Insulin, nmol/l</td>
</tr>
<tr>
<td></td>
<td>C-peptide, nmol/l</td>
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<tr>
<td></td>
<td>M, mg·kg⁻¹·min⁻¹</td>
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<tr>
<td>Study D</td>
<td>Glucose, mmol/l</td>
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<tr>
<td></td>
<td>cv glucose, %</td>
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<tr>
<td></td>
<td>Insulin, nmol/l</td>
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<tr>
<td></td>
<td>C-peptide, nmol/l</td>
</tr>
<tr>
<td></td>
<td>M, mg·kg⁻¹·min⁻¹</td>
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</tbody>
</table>

Alterations in the plasma concentrations of glucose, insulin and C-peptide as well as the glucose disposal rate (M) under basal conditions and during clamp studies at different plasma glucose levels and insulin infusion rates (Study A 3.3, Study B 6.6, Study C 13.3 and Study D 27.0 µmol·kg⁻¹·min⁻¹). The cv of plasma insulin varied between 11 and 26%. Data are given as means ± sd. Mean values are calculated for basal conditions and for the last 60 min of each clamp period. Statistical differences were calculated between the basal state and the clamp study (glucose, insulin, C-peptide) or between eu- and hyperglycemic clamps (*P < 0.001).

In order to evaluate the effect of low insulin infusion rates on endogenous glucose production, plasma glucose was clamped at the basal level (5.2 mmol/l) and reached a mean value of 5.1 ± 0.2 mmol/l (cv: 4.3%). At a low insulin infusion rate, plasma insulin reached a steady state level of 0.28 nmol/l and was increased up to 0.55 nmol/l at an infusion rate of 6.6 pmol·kg⁻¹·min⁻¹. In the basal state, the rate of glucose appearance (Ra) was 2.10 mg·kg⁻¹·min⁻¹. The total isotopically determined rate of glucose appearance (i.e. endogenous + exogenous) increased to 3.60 and 7.15 mg·kg⁻¹·min⁻¹. Since M was 3.21 and 6.89 mg·kg⁻¹·min⁻¹,
Fig. 2.
Glucose disposal rate ($M$) as a function of the plasma glucose level. Plasma glucose concentration: ○ 4.7, ● 6.7, Δ 9.7 mmol/l. Individual data were correlated and r-values were estimated to be 0.81 at 4.7 mmol/l, 0.67 at 6.7 mmol/l, and 0.67 at 9.7 mmol/l ($P < 0.001$ and $P < 0.005$).

Fig. 3.
Lineweaver Burke analyses of the effect of hyperglycemia on insulin-induced glucose disposal. For the original data see Fig. 2. The r-values were obtained to be 0.71 at 4.7 mmol/l ($V_{\text{max}}$: 12.4 mg·kg$^{-1}$·min$^{-1}$, $K_m$: 0.45 nmol/l), 0.72 at 6.7 mmol/l ($V_{\text{max}}$: 19.3 mg·kg$^{-1}$·min$^{-1}$, $K_m$: 0.52 nmol/l), and 0.67 at 9.8 mmol/l ($V_{\text{max}}$: 26.4 mg·kg$^{-1}$·min$^{-1}$, $K_m$: 0.29 nmol/l) ($P < 0.001$ and $P < 0.005$).
endogenous Ra was calculated to be 0.39 and 0.26 mg·kg⁻¹·min⁻¹. Thus, endogenous Ra was decreased to 20% and 10% of its basal level during the different insulin infusion and euglycemia.

Study 3
During euglycemia and hyperinsulinemia (Study 3A) M increased from 6.3 (30–60 min) to 9.5 (180–240 min) mg·kg⁻¹·min⁻¹. Thus, M increased by 9 to 11% per h (Table 3). During hyperglycemia and hyperinsulinemia (Study 3B) plasma C-peptide decreased and M increased from 13.3 (30–60 min) to 16.5 (180–240 min) mg·kg⁻¹·min⁻¹, which is an increase of about 6 to 10% per h (Table 3).

Discussion
The essential findings of the present study are: insulin and hyperglycemia both increase glucose disposal rate (Table 2, Fig. 1) and hyperglycemia increases insulin responsiveness and it decreases the insulin concentration causing a half maximal stimulation of glucose disposal (Figs. 2 and 3).

Concerning the former results our data confirm previous studies using different clamp protocols (Best et al. 1981; DeFronzo & Ferrannini 1982; Proietto et al. 1983; Gottesman et al. 1984; Jackson et al. 1986; Yki-Järvinen et al. 1987), whereas the latter results extend our present view and fits to recent in vitro data (Arner et al. 1983; Livingston et al. 1984). There is good evidence that insulin and glucose exert separate effects on glucose uptake (Jackson et al. 1986; Yki-Järvinen et al. 1987). To correct for the effect of glucose per se, the MCR for glucose or the 'insulin sensitivity index' have been proposed to reflect insulin action at least under physiological conditions (Dobler et al. 1981; DeFronzo & Ferrannini 1982; Proietto et al. 1983; Radziuk & Lickley 1985). This concept has been questioned recently (Gottesman et al. 1984). Our data clearly show that neither M, the M/I-ratio, the MCR for glucose nor the insulin sensitivity index are independent of the plasma glucose level (Table 2, Results). Thus, all these parameters seem to be less useful measures of hormonally regulated glucose disposal.

<table>
<thead>
<tr>
<th>Study A</th>
<th>Study B</th>
</tr>
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<tbody>
<tr>
<td>Glucose, mmol/l</td>
<td>5.1 ± 0.3</td>
</tr>
<tr>
<td>CV glucose, %</td>
<td>4.2 ± 1.2</td>
</tr>
<tr>
<td>Insulin, nmol/l</td>
<td>0.15 ± 0.24</td>
</tr>
<tr>
<td>C-peptide, nmol/l</td>
<td>1.01 ± 0.07</td>
</tr>
<tr>
<td>M, mg·kg⁻¹·min⁻¹</td>
<td>4.7 ± 0.1</td>
</tr>
</tbody>
</table>

Table 3. Effect of prolonged clamp studies at eu- and hyperglycemia on insulin-induced glucose disposal rate (M).

Data from Study 3A and 3B during clamp studies (min)

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>30–60</th>
<th>60–120</th>
<th>120–180</th>
<th>180–240</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mmol/l</td>
<td>5.1 ± 0.3</td>
<td>4.7 ± 0.2</td>
<td>4.7 ± 0.1</td>
<td>4.7 ± 0.1</td>
<td>4.7 ± 0.2</td>
</tr>
<tr>
<td>CV glucose, %</td>
<td>4.2 ± 1.2</td>
<td>6.3 ± 1.1</td>
<td>7.8 ± 1.2</td>
<td>8.7 ± 1.4</td>
<td>9.5 ± 1.4</td>
</tr>
<tr>
<td>Insulin, nmol/l</td>
<td>0.15 ± 0.24</td>
<td>0.67 ± 0.14</td>
<td>0.69 ± 0.10</td>
<td>0.71 ± 0.15</td>
<td>0.71 ± 0.09</td>
</tr>
<tr>
<td>C-peptide, nmol/l</td>
<td>1.01 ± 0.07</td>
<td>0.61 ± 0.07</td>
<td>0.54 ± 0.05</td>
<td>0.53 ± 0.05</td>
<td>0.49 ± 0.02</td>
</tr>
<tr>
<td>M, mg·kg⁻¹·min⁻¹</td>
<td>6.3 ± 1.1</td>
<td>7.8 ± 1.2</td>
<td>8.7 ± 1.4</td>
<td>9.5 ± 1.4</td>
<td>13.3 ± 1.7</td>
</tr>
</tbody>
</table>

Thus, changes in euglycemia and hyperglycemia and hyperinsulinemia influence glucose disposal in a similar way as changes in plasma insulin concentration affect glucose disposal during an insulin infusion. Hence, the human and rat model fit well to the hyperinsulinemic-euglycemic clamp studies. The results correlate well with previous findings on glucose uptake and disposal during insulin infusions and during euglycemic and hyperglycemic clamp studies.
A prolonged clamp protocol was used in our study, which may affect the data. The problem becomes evident, if one compares M-values obtained at an insulin infusion rate of 6.6 pmol·kg\(^{-1}\)·min\(^{-1}\) and hyperglycemia (9.5 mmol/l) during the first (Study 3B, Table 3) and the last period (Study 1B, Table 2) of the clamp protocol: M varied between 14.2 and 19.6 mg·kg\(^{-1}\)·min\(^{-1}\). The calculation based on a 10% increase per hour owing to the prolonged clamp itself (Table 3) may explain this difference. The effect might be explained by an insulin-induced increase in the distribution volume for glucose (Ferrannini et al. 1985). Since increases in M owing to alterations in the distribution volume do not reflect an increased glucose utilization, this possibility implicates a pitfall in the interpretation of M-values obtained during prolonged clamps. However, recalculation of our data corrected for a 10% increase per hour again showed that hyperglycemia increases V\(_{\text{max}}\) (i.e. 13.4 at euglycemia and 20.0 mg·kg\(^{-1}\)·min\(^{-1}\) at 9.5 mmol/l, but decreases K\(_{\text{m}}\) (i.e. 0.53 nmol/l at 4.5 mmol/l and 0.28 nmol/l at 9.5 mmol/l). Consequently, this does not affect the significance of the data. Nevertheless, comparing the percentage increase in M (euglycemia vs hyperglycemia in Study 1B and 3A vs 3B), the difference between the two protocols becomes apparent, i.e. +202% (Study 1B) vs +82% (Study 3A vs 3B at 60–120 min).

Hyperglycemia induces a disproportionate increase in portal venous vs arterial insulin and this occurs despite exogenous insulin infusion (Bratusch-Marrain & Waldhäusl 1985; Christin et al. 1986). Therefore, somatostatin was infused throughout the studies, which may also influence tissue insulin sensitivity (Bergman et al. 1985). Comparing our recent data with euglycemic clamp data from previous experiments (Müller et al. 1986), it becomes evident that somatostatin decreases the absolute amount of M by about 11 to 22%, which does not affect the significance of our data.

The correlation between plasma insulin and M fitted straight lines within the physiological hormone concentration range (Figs. 2 and 3). This finding is rather surprising for several reasons. The glucose clamp technique measures a net metabolic event, i.e. the decrease in hepatic glucose production plus the increase in total body glucose disposal, which results from glucose transfer across plasma membranes as well as from intracellular glucose metabolism. Since both glucose and insulin are known to inhibit hepatic glucose output (Müller et al. 1988a), this will affect data obtained using different clamp protocols. In addition different mechanisms are known to regulate glucose transport, e.g. active transport, carrier-mediated facilitated diffusion and free diffusion. Under clamp conditions, total body glucose uptake can be mainly considered as facilitated diffusion, because most of the glucose infused is taken up by the muscles (DeFronzo et al. 1981; Ferrannini et al. 1985; Jackson et al. 1986). Muscle glucose uptake occurs via a stereospecific transport system, which displays saturation kinetics and may be described in terms of Michaelis Menten kinetics (Gottesman et al. 1984). Under physiological conditions, glucose transport is not saturated and intracellular free glucose concentration is low as far as transport does not exceed phosphorylation within the cell. Then transport is rate-limiting for cellular glucose metabolism and may be considered as an one enzyme/one substrate reaction. However, even at physiological plasma glucose, maximally stimulating insulin shifts the rate-limiting step from glucose transport to some step beyond transport (Ferrannini et al. 1985; Kubo & Foley 1986; Yki-Järvinen et al. 1987). Then phosphorylation of glucose becomes rate-limiting and part of the glucose flows back out of the cell. From this it is obvious that glucose disposal results from different kinetics in the distribution and disposition of glucose (Ferrannini et al. 1985).

With respect to intracellular metabolic events, glucose is metabolized via oxidative and/or non-oxidative pathways of intermediary metabolism. Insulin increases glucose oxidation as well as glucose storage (Śeitz et al. 1977a,b). Oxidation and storage equally contribute to total glucose disposal under postabsorptive and near physiologic hyperinsulinemic conditions, whereas further increasing plasma insulin as well as hyperglycemia both increase glucose disposal by mainly stimulating non-oxidative metabolism (Jacot et al. 1982). This finding implicates that distinct alterations in oxidative or non-oxidative glucose metabolism become obvious at different clamp protocols, e.g. hyperthyroidism increases M at euglycemia (i.e. oxidation is increased), but is without effect or decreases M at hyperglycemia (i.e. storage is decreased; Randin et al. 1985; Müller et al. 1986; Müller et al. 1987b).
A simple euglycemic clamp protocol alone gives only limited information, because insulin as well as glucose increase glucose disposal, and insulin action depends on the prevailing glucose concentration. From our data we conclude that clamp studies should be performed at least at two different plasma glucose levels. If distinctive alterations are observed, more sophisticated techniques should be applied (e.g. isotope dilution, catheter techniques or indirect calorimetry).

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References


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