Mechanisms of glucose intolerance during triglyceride infusion

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Mechanisms of glucose intolerance during triglyceride infusion. Am. J. Physiol. 275 (Endocrinol. Metab. 38): E641–E648, 1998.—Lipid infusions may affect glucose tolerance by effects on glucose production or utilization. We performed double-labeled oral glucose tolerance tests with and without a lipid infusion in eight normal subjects. During the lipid infusion, plasma glucose and insulin levels were higher, showing some insulin resistance. The increased glucose level was due to a higher total glucose appearance rate, partly reproducible by a control infusion of glycerol [saline 1,181 ± 71 mg·kg⁻¹·330 min⁻¹ vs. lipid 1,388 ± 100 (P < 0.05) vs. glycerol 1,276 ± 126 (NS)].

The tracer-determined appearance rate of exogenous glucose was higher with lipid infusion but was probably overestimated because of higher ¹³C recycling into glucose. Residual systemic glucose production was increased but was reproducible by the glycerol infusion. Total glucose disposal was increased. This was observed despite a lower stimulation of total glucose oxidation as measured by indirect calorimetry, whereas oxidation of exogenous glucose was normal after correction for the lipid-induced modification of excretion rate of ¹³C. Accordingly, glucose nonoxidative disposal was increased. These moderate modifications of glucose metabolism (increased appearance, increased nonoxidative disposal, and lower total oxidation) have been reported in starvation-induced or spontaneously impaired glucose tolerance. Further impairment, especially decreased nonoxidative glucose disposal, seems to be required to produce non-insulin-dependent diabetes mellitus.

oral glucose tolerance; Randle cycle; systemic glucose production; glucose disposal; glucose recycling

More than thirty years ago, Randle et al. (33) showed that increased availability of lipid substrates reduced glucose utilization, which was thought to play a role in insulin-resistant states, such as obesity, diabetes, or starvation. Numerous studies examining the influence of lipid infusions on glucose metabolism have since been devoted to the “glucose-free fatty acid cycle” in humans.

Lipid infusions have been found to have little effect in the postabsorptive state (8) unless insulin secretion is disrupted as in normal subjects by infusion of somatostatin (5) or in patients with non-insulin-dependent diabetes mellitus (NIDDM) (35). On the other hand, both insulin-stimulated glucose oxidation and nonoxidative disposal (6, 7) are impaired by infusion of lipids during euglycemic hyperinsulinemic clamp. However, these observations of lipid-induced insulin resistance in situations of euglycemia do not necessarily imply that lipid-carbohydrate interactions play a significant role in the alterations of glucose metabolism observed in the postprandial state of insulin-resistant subjects, since plasma glucose levels are increased in the latter case. Effects of lipid infusions may be more relevant if tested under the conditions of the oral glucose tolerance test (OGTT), which is closer to the postprandial state.

The influence of a lipid infusion on glucose tolerance has been studied by Rousselle et al. (37) and Kruszynska et al. (23) in normal subjects and Meylan et al. (26) in obese subjects. In these studies, lipids inhibited glucose oxidation, although glucose nonoxidative disposal was increased, presumably due to the slight increase in glycemia. However, indirect calorimetry may lead to erroneous conclusions concerning glucose oxidation when lipids are infused, since they stimulate gluconeogenesis (9, 10), which could result in an underestimate of glucose oxidation if amino acids are the main gluconeogenic precursors used (14). The study from Kruszynska et al. (23) suggested that lipid infusion also induced a defective suppression of systemic glucose production (SGP), as observed during clamp studies with lipid infusion (24), but the potential role of the glycerol infused was not evaluated in this observation.

In the present study, we performed double-labeled OGTTs with a naturally ¹³C-enriched oral load (cornstarch glucose; Ref. 41) and a deuterated glucose infusion in eight normal volunteers. Each subject was studied twice, once during a saline infusion (controls) and once during a lipid infusion. To determine the influence of glycerol in the infused lipid emulsion on glucose appearance, four subjects were studied a third time, during a glycerol infusion. Four subjects also underwent a lipid infusion without OGTT to assess the contribution of ¹³C from infused lipids to expired ¹³CO₂. Using this methodology, we could determine the respective contribution of modifications in SGP, glucose oxidation, and nonoxidative disposal to lipid-induced alteration of glucose tolerance.

Methods

Materials: D-[6,6-²H₂]glucose (99 atom% excess) was obtained from the Commissariat à l’Energie Atomique (Gif-sur-Yvette, France). It was checked to be sterile and pyrogen free and was dissolved in sterile normal saline solution before...
administration. Pure cornstarch glucose was obtained from Aguetant (Lyon, France). The triglyceride emulsion (Ivélip, 20%) was obtained from Cernep Synthélabo (Montargis, France). It contained 200 g/l long-chain triglycerides (fatty acids: 11% palmitic acid, 5% stearic acid, 26% oleic acid, 50% linoleic acid, 7% linolenic acid, 0.5% gadoleic acid, and 0.5% erucic acid) and 25 g/l glycerol to stabilize the emulsion. The 100 g/l glycerol solution was obtained from the Pharmacie Centrales des Hôpitaux de Bordeaux. Gas exchanges were measured using a Deltatrac metabolic monitor (Datex, France).

Subjects. Eight subjects were studied twice by doubly labeled OGTTs, once under infusion of saline (control tests) and once under a lipoid infusion (Ivélip tests) 1 mo later. Four of these subjects had two more tests: one OGTT under a glycerol infusion and one lipid infusion (Ivélip) without OGTT. They were normal healthy volunteers (5 men and 3 women, age 23 ± 2 yr, body weight 63.2 ± 6.2 kg, body mass index 21.5 ± 0.4). None of them had a history of diabetes or other diseases. They were requested to consume their normal diet but to avoid food containing cane sugar, cornstarch, or exotic fruits for 1 wk before and between the tests. They gave their written consent to the study after being informed of its nature, purpose, and potential risks. The protocol was approved by the Ethical Committee of Edouard Herriot Hospital (Lyon, France).

Protocol. Figure 1 shows the study design. All subjects were studied in the postabsorptive state after a 12-h overnight fast in the metabolic unit of the Service de Nutrition-Diabétologie (Hôpital Haut-Levêque, Pessac, France). A retrograde catheter was inserted in a dorsal hand vein and kept in a hot blanket (55°C) to collect arterialized venous blood. A forearm vein of the contralateral arm was catheterized to infuse D-[6,6-2H2]glucose and saline, Ivélip, or glycerol.

A priming dose of D-[6,6-2H2]glucose (6 mg/kg) was administered at 0800, and D-[6,6-2H2]glucose was then infused at a constant rate (0.06 mg·kg⁻¹·min⁻¹) using an electric syringe (Harvard, Les Ulis, France) for 450 min. Half an hour later, a constant-rate infusion (0.015 ml·kg⁻¹·min⁻¹) as used in previous studies (Refs. 24, 35) of saline (control tests) or Ivélip (Ivélip tests) began and was continued until the end of the test by using a volumetric infusion pump (Harvard). Because heparin has its own effects on insulin binding and biological activity, we did not use it in combination with the lipid infusion (21). Four subjects underwent a third test with a constant-rate infusion (0.004 ml·kg⁻¹·min⁻¹) of a 100 g/l glycerol solution to test the effect on glucose appearance of the glycerol used in the triglyceride emulsion. The first 120 min of the tests (from times −120 to 0) were allowed for isotopic equilibration and measurement of postabsorptive glucose turnover rate. Thereafter, a dose of 1 g/kg of naturally 13C-enriched cornstarch glucose, diluted in water (30 g/100 ml), was ingested.

In four subjects, the effect of the Ivélip infusion alone (0.015 ml·kg⁻¹·min⁻¹ during 420 min, without OGTT) on 13C enrichment of expired CO2 was determined to allow calculation of a corrected exogenous glucose oxidation rate (Gexo corr).

Throughout the test, samples of blood and of expired gases were drawn for determination of metabolites and hormone levels and for isotopic enrichments. Except during the glycerol infusion (which was designed to study glucose appearance), gaseous exchange was measured continuously using the Deltatrac metabolic monitor, with a 5-min pause every 30 min to collect expired gases for isotopic enrichment. Urine samples were collected at times −120, 0, and 330 for urinary nitrogen excretion determination.

Analytical procedures. Plasma glucose, free fatty acids (FFA) (25), glycerol, and triglyceride concentrations were determined enzymatically (2). Urinary nitrogen was determined by the Kjeldahl method. Insulin and C-peptide levels were measured by RIA. Plasma D-[6,6-2H2]glucose enrichment was measured by conventional selected ion-monitoring gas chromatography-mass spectrometry (Hewlett-Packard 5971A-MSD, Paris, France) as described by Bier et al. (3). Plasma and ingested [13C]glucose isotopic enrichment was measured by gas chromatography-isotope ratio mass spectrometry (Sira 12, VG Instrument, Middlewich, UK) as described by Tissot et al. (41). 13C enrichment of expired CO2 was determined on the dual-inlet isotope ratio mass spectrometer described by Guilluy et al. (19). The 13C-to-12C ratios of the samples were expressed as differences from the International PDB standard according to the formula, δ13Cp = [(13C/12C sample − 13C/12C standard)]/(13C/12C standard) × 1,000, and was transformed to atom percent excess (APE) for ingested and plasma glucose as previously described (41).

To determine the relative 13C abundance of glucose, glycerol, and lipid emulsions, samples of these solutions were compartmented at 1,020°C. The CO2 was separated using a liquid N2 trap and analyzed for 13C abundance in 13C enrichment of expired CO2 was determined on the dual-inlet isotope ratio mass spectrometer described by Guilluy et al. (19). The 13C-to-12C ratios of the samples were expressed as differences from the International PDB standard according to the formula, δ13Cp = [(13C/12C sample − 13C/12C standard)]/(13C/12C standard) × 1,000, and was transformed to atom percent excess (APE) for ingested and plasma glucose as previously described (41).
The exogenous glucose oxidation rate ($G_{exo}$, mg·kg$^{-1}$·min$^{-1}$) appeared from the whole organism, as calculated in previous studies, which is a balance between glucose input and glucose disappearance for the contribution of $^{13}$C from the lipid infusion, since the infused lipids must be oxidized before their $^{13}$C appears in exhaled CO$_2$, and such oxidation will tend to be reduced during the OGTT (38).

Glucose nonoxidative disposal was calculated using three different relationships

$$G_{non-Ox1} = G_{Ingested} - G_{OxSB}$$

which is a balance between glucose input and glucose disappearing from the whole organism, as calculated in previous

$$G_{non-Ox2} = R_{at} - G_{Ox}$$

as proposed by Féry et al. (17), which represents nonoxidized glucose leaving plasma, and takes account of lipid-induced changes in glucose turnover rate

$$G_{non-Ox3} = R_{de} - G_{exo}$$

which represents exogenous glucose which had left plasma but did not contribute to exhaled CO$_2$ and is not affected by lipid-induced alterations in gluconeogenesis, since it is not based on the indirect calorimetric measurements. $G_{non-Ox3,corr}$ was also calculated, $G_{non-Ox3,corr} = R_{de} - G_{eco,corr}$. Turnover and oxidation rates values were calculated for 30-min intervals; cumulative values for the whole OGTT (330 min) are also presented.

Statistical analysis. Results are shown as means ± SE. Comparisons were performed by one-way ANOVA for repeated measurements followed by a t-test (within test comparison) and a t-test for nonpaired data (between test comparison). $P < 0.05$ was considered significant.

RESULTS

Substrates and hormones. The data for substrates and hormones are presented in Figs. 2 and 3. The lipid infusion induced a continuous rise in plasma triglycerides and prevented the fall in FFA during the OGTT. Triglycerides and FFA were significantly higher from the beginning to the end of the lipid infusion, except at the last time point ($>330$ min), when FFA did not differ between the saline and IV-ELIP tests. Plasma glucose levels did not differ before the tests (times $<30$ and $<90$) and even before the oral load, after 90 min of lipid infusion. The lipid infusion induced a slight impairment in glucose tolerance, as shown by significantly higher values from times $>120$ to $>180$ ($P < 0.05$). Insulin and C-peptide levels were also slightly higher during the lipid infusion, with significant differences from times $>180$ to $>240$ ($P < 0.05$). The glycerol infusion had no significant effect on any substrate or hormone level, except on plasma glycerol, which was higher than during the saline infusion from times $>120$ to the end of the test ($P < 0.05$). However, this increase was less important than that observed during the lipid infusion ($P < 0.05$ from times $>30$ to $>300$).

Isotopic enrichments. Isotopic enrichment data are given in Fig. 4. d-[6,6-D$_2$]glucose enrichments declined comparably during the OGTT under saline, glycerol, and lipid infusion, reverting to postabsorptive values at the end of tests. However, as shown in Fig. 4, there was a trend for lower values under IV-ELIP. Before the oral load was ingested, no differences in the $^{13}$C level in glucose were detected among the saline, glycerol, and lipid infusion tests. It rose during the first 2 h of the
OGTT and then declined without returning to baseline at the end of the tests. This decrease was slower during the lipid infusion, with significantly higher $^{13}$C enrichments of plasma glucose at times 180, 210, 240, 300 (P < 0.05), and 330 (P < 0.01). During glycerol infusion, $^{13}$C enrichments of plasma glucose were lower (P < 0.05 at times +60, 90, and 120). $^{13}$C enrichment of expired CO$_2$ was significantly lower during the last 150 min of the IvErip tests than during control tests (P < 0.01).

Fig. 2. Time course of plasma glucose (mM), insulin (pM), and C-peptide (nM) before (times −120 to 0 min) and after (times 0 to 330 min) oral load. ○, Controls; ●, IvErip tests; ▲, glycerol tests. *P < 0.05 between IvErip and saline controls.

Fig. 3. Time course of plasma glycerol (µM), free fatty acid (FFA, µM), and triglycerides levels (mM) before (times −120 to 0 min) and after (times 0 to 330 min) oral load. ○, Controls; ●, IvErip tests; ▲, glycerol tests. *P < 0.05 between IvErip and saline controls.
However, the infusion of Ivelip alone in four subjects produced a progressive decline in 13C enrichment of expired CO2, with values from time 0 to 120 (P < 0.05). As shown in Fig. 4, no difference in 13C enrichment of expired CO2 was found between the Ivelip and saline tests after correction for the contribution of 13C from the infused lipids.

Rates of glucose appearance. Rates of glucose appearance are given in Table 1. Before the OGTT, postabsorptive SGP rates were identical during control (2.32 ± 0.11 mg·kg⁻¹·min⁻¹), Ivelip (2.32 ± 0.05 mg·kg⁻¹·min⁻¹), and glycerol (2.46 ± 0.18 mg·kg⁻¹·min⁻¹) tests. Cumulative RaT over 330 min were higher during the lipid infusion and slightly increased during the glycerol infusion [saline 1,181 ± 71 mg/kg vs. Ivelip 1,388 ± 100 mg/kg (P < 0.05), glycerol 1,276 ± 126 mg/kg (NS vs. saline)]. Cumulative RaE over 330 min were higher during the lipid infusion and lower during the glycerol infusion [saline 864 ± 38 mg/kg vs. Ivelip 993 ± 67 mg/kg (P < 0.05), glycerol 698 ± 117 mg/kg (P < 0.05 vs. saline)]. Cumulative SGP over 330 min were higher during the lipid and glycerol infusions [saline 317 ± 57 mg/kg vs. Ivelip 395 ± 58 mg/kg (P < 0.05), glycerol 570 ± 54 mg/kg (P < 0.05 vs. Ivelip and P < 0.001 vs. saline)].

Rates of glucose disappearance. Rates of glucose disappearance are given in Table 1. No glucose was detected in urine in any of the tests. Cumulative RdT over 330 min were higher during the lipid infusion (saline 1,242 ± 67 mg/kg vs. Ivelip 1,401 ± 96 mg/kg; P < 0.05). This was also observed for RdE but did not reach significance (saline 810 ± 52 mg/kg vs. Ivelip 885 ± 72 mg/kg; NS). Cumulative GOx over 330 min was lower during lipid infusion (saline 645 ± 19 mg/kg vs. Ivelip 405 ± 33 mg/kg; P < 0.001). This was also observed for Gexo (saline 423 ± 39 mg/kg vs. Ivelip 266 ± 60 mg/kg; P < 0.05), but the difference was

Table 1. Glucose fluxes and oxidation during oral glucose tolerance test

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>Ivelip</th>
<th>P</th>
<th>Glycerol</th>
<th>P</th>
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<tr>
<td>Rates of appearance</td>
<td></td>
<td></td>
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<tr>
<td>Total glucose</td>
<td>1,181±71</td>
<td>1,388±100</td>
<td>0.03</td>
<td>1,276±126</td>
<td>NS</td>
</tr>
<tr>
<td>Exogenous glucose</td>
<td>864±38</td>
<td>993±67</td>
<td>0.03</td>
<td>698±117</td>
<td>0.04</td>
</tr>
<tr>
<td>Systemic glucose production</td>
<td>317±57</td>
<td>395±58</td>
<td>0.04</td>
<td>570±54</td>
<td>0.03</td>
</tr>
<tr>
<td>Rates of disappearance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total glucose</td>
<td>1,242±67</td>
<td>1,401±96</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exogenous glucose</td>
<td>810±52</td>
<td>885±72</td>
<td>0.24</td>
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<tr>
<td>Total oxidation (indirect calorimetry)</td>
<td>645±19</td>
<td>405±33</td>
<td>0.0002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exogenous glucose</td>
<td>423±35</td>
<td>266±60</td>
<td>0.02</td>
<td>(Corr, (Corr, NS)</td>
<td></td>
</tr>
<tr>
<td>Systemic glucose (13C excretion in CO2)</td>
<td>666±51</td>
<td>806±28</td>
<td>0.03</td>
<td></td>
<td></td>
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<tr>
<td>Gnon-Ox1</td>
<td>597±78</td>
<td>996±55</td>
<td>0.0007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gnon-Ox2</td>
<td>392±100</td>
<td>619±95</td>
<td>0.0002</td>
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<tr>
<td>Gnon-Ox3</td>
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</table>

Values are means ± SE expressed in mg·kg⁻¹·330 min⁻¹. P values indicate differences vs. saline. Oral load was 1,000 mg/kg. Gnon-Ox1, Gnon-Ox2, Gnon-Ox3, glucose nonoxidative disposal calculated by 3 different relationships (see text).
smaller and was abolished by correction for the contribution of $^{13}$C from the lipids ($G_{\text{exo,corr}}$: 360 ± 92 mg/kg; NS vs. saline). Although different results were obtained from the three different relationships used to calculate nonoxidative glucose disposal, in every case the values were significantly higher with the lipid infusion ($G_{\text{non-oxic}}$: saline 666 ± 51 mg/kg vs. Ivélip 806 ± 28 mg/kg, $P < 0.05$; $G_{\text{non-oxic}}$: saline 597 ± 78 mg/kg vs. Ivélip 996 ± 0.95 mg/kg, $P < 0.001$; $G_{\text{non-oxic}}$: saline 392 ± 100 mg/kg vs. Ivélip 619 ± 95 mg/kg, $P < 0.001$). This was also true when $G_{\text{exox}}$ was used in place of $G_{\text{exo}}$ ($G_{\text{non-oxic,corr}}$: 545 ± 83 mg/kg; $P < 0.05$ vs. saline).

**DISCUSSION**

The present study was designed to shed more light on the mechanism of the moderate glucose intolerance induced by a lipid infusion during an OGTT. The results of our control OGTTs are in agreement with those of other studies using the same duration (5–6 h) and 1 g/kg oral glucose load (16, 27, 41). In line with Rousselle et al. (37) and Kruszynska et al. (23), we found that lipid infusion produced a moderate glucose intolerance. This was due to a higher rate of total glucose appearance, an impairment in the suppression of EGP, and an apparent higher appearance of exogenous glucose. The higher rate of total glucose appearance was partially reproducible by a glycerol infusion. The total glucose disappearance rate was also higher during lipid infusion despite a decrease in glucose oxidation, due to an increase in nonoxidative disposal. Total glucose oxidation, evaluated by indirect calorimetry, was more inhibited than exogenous glucose oxidation evaluated by the recovery of $^{13}$C in exhaled CO$_2$. Although nonoxidative glucose disposal was only evaluated indirectly, the three different methods of calculation led to the same conclusion.

The slight defect in the suppression of SGP induced by the lipid infusion was observed despite slightly higher plasma levels of insulin and glucose, which are known to suppress SGP (11). This demonstrates that lipids can produce a state of hepatic resistance to insulin (24) but also resistance to the suppressive effect of glucose. This effect (395 – 317 = 78 mg·kg$^{-1}·$330 min$^{-1}$) seems moderate, but it was probably underestimated. SGP was calculated by substracting $R_{\text{aE}}$ from $R_{\text{dT}}$. We found an increased $R_{\text{aE}}$ under lipid infusion. This unexpected finding might reflect a higher absorption of glucose by the gut as proposed by Meylan et al. (26) but has yet to be demonstrated. Lipid infusion could also have, contrary to the total body glucose uptake, lowered the splanchnic uptake of the oral load. In fact, peripheral and splanchnic glucose uptake have been shown to be regulated differently (11). However, this would not explain why the lipid-induced increase in $R_{\text{aE}}$ only appeared at the end of the tests (times +150 to +240). In agreement with the results of Tissot et al. (41), calculated $R_{\text{aE}}$ remains positive 330 min after the oral load had been ingested in our control tests (0.65 ± 0.22 mg·kg$^{-1}·$min$^{-1}$), when all metabolic parameters had returned to initial values. At this time, glucose is no longer absorbed (1), and the persistence of a significant enrichment in $^{13}$C of plasma glucose is an indication of recycling of the label through the gluconeogenic pathway. This rate of recycling has been estimated to be $\sim$10% of the metabolism of the glucose load (15). It could have been increased by the lipid infusion, since FFA can stimulate gluconeogenesis. Indeed Clore et al. (10) have demonstrated that the activity of the Cori cycle can be doubled by a lipid-heparin infusion in normal subjects. It is thus quite possible that an enhanced gluconeogenesis during lipid infusion led to an increased recycling of the $^{13}$C label, giving an erroneously high $R_{\text{aE}}$ and an underestimate of the calculated SGP ($SGP = R_{\text{dT}} - R_{\text{aE}}$).

Lipid emulsions contain free glycerol, which could contribute to the enhanced SGP. Had all this glycerol been used for gluconeogenesis, it would represent a production of 62 mg·kg$^{-1}·$330 min$^{-1}$ glucose, thus explaining the main part of the increased SGP (78 mg·kg$^{-1}·$330 min$^{-1}$). However, only 45–50% of infused glycerol is converted to glucose, even at high rates of glycerol infusion (31). It is unlikely that this proportion was increased by the presence of high FFA levels, since glycerol metabolism already generates NADH. To solve this issue, we performed glucose tolerance tests with glycerol infusion. As shown in Fig. 3, plasma glycerol rose only slowly compared with an almost square-wave rise in concentration during Ivélip infusion. Presumably, during Ivélip infusion, glycerol is released from the infused triglycerides by the action of lipoprotein lipase in peripheral tissues, which also explains the rise in FFA. A primed infusion of glycerol, with a higher infusion rate, would therefore be necessary to match the systemic glycerol concentrations seen during Ivélip infusion. However, important effects on glucose metabolism were observed during our glycerol infusion. We observed a moderate increase in glucose $R_{\text{dT}}$: $R_{\text{aE}}$ was surprisingly low and therefore calculated SGP high. In fact, the increase in SGP compared with saline glucose tolerance tests cannot be accounted for by the infused glycerol. The $^{13}$C abundance in this glycerol was only slightly less than in the glycerol present in the lipid emulsion infused (−30.2 vs. −29.5$^{13}$C$_{3}$ × 1,000). Thus this cannot explain why $^{13}$C abundance in plasma glucose during the OGTT with glycerol infusion was so low. We think that, in the absence of high FFA levels, the recycling of $^{13}$C glucose through gluconeogenesis from $^{13}$C-lactate was decreased by the glycerol infusion. This possibility is supported by previous demonstrations that glycerol infusion inhibits gluconeogenesis from other precursors (20, 40). Whatever the exact mechanism, this makes difficult to quantify accurately the contribution of glycerol to SGP. It is probable that the higher glucose $R_{\text{dT}}$ which we found during glycerol infusion reflects an enhanced SGP. We therefore think, in accordance with results from Boden and Chen (4), that the glycerol content of the lipid emulsion probably played a role in the modification of SGP.

$R_{\text{dT}}$ was not evaluated in previous studies on lipid-induced glucose intolerance (26, 37), except for the study of Kruszynska et al. (23). In agreement with this last study, we found that the lipid infusion increased glucose $R_{\text{dT}}$ during OGTT. This contrasts with results obtained during hyperinsulinemic euglycemic clamps.
(24). Using the glucose-clamp technique, Boden et al. (6) and Bonadonna et al. (7) have shown that a lipid infusion takes 3–4 h to inhibit glucose uptake. This may account for the failure to observe an inhibitory effect of lipids on glucose uptake in some studies but not in the present one, since we infused lipids for 7 h (beginning 90 min before glucose ingestion) and $R_{\text{ET}}$ was higher at the end of the IVe `lip tests. Increased plasma insulin and glucose levels are recognized stimulators of peripheral glucose uptake (11). This may well account for the higher $R_{\text{ET}}$ we found; plasma insulin and glucose levels were significantly higher under lipid infusion in our study (which was not the case in clamp experiments). This higher $R_{\text{ET}}$ was observed despite a decrease in glucose oxidation as determined by indirect calorimetry, which is an early and consistent consequence of a lipid infusion (4, 6, 23, 24, 26, 37). Measurement of expired $^{13}$CO$_2$ can also be used to measure glucose oxidation after an oral glucose load enriched with $[^{13}$C]glucose. At first glance, both techniques gave the same result: the lipid infusion led to a $\sim$40% inhibition in $G_{\text{Ox}}$ and $G_{\text{exo}}$. However, the lipid infusion had a low abundance in $^{13}$C, which had its own effect on $^{13}$CO$_2$ excretion rate independent of any lipid-glucose interaction, as we noted in the four subjects studied without the oral glucose load. Correction for this effect abolished the apparent inhibitory effect of the lipid infusion on $G_{\text{exo}}$. This subtraction of the effect of the lipid infusion alone on $^{13}$CO$_2$ excretion is maximal estimate of the correction, since it does not take account the decrease of lipid oxidation due to enhanced glucose metabolism during the OGTT (38). However, our result suggests that the inhibitory effect of lipid infusion is more pronounced on total than on exogenous glucose oxidation. It may therefore specially affect the rate of glycogen oxidation. Because glycogen oxidation is decreased or unchanged depending on the method used, the higher $R_{\text{ET}}$ during lipid infusion appears to derive from an increase in nonoxidative disposal of glucose. This increase was significant regardless of the method of calculation ($G_{\text{non-Ox1}} \approx +20\%$, $G_{\text{non-Ox2}}$ and $G_{\text{non-Ox3}} \approx +40\%$). Because it does not take account of the higher $R_{\text{ET}}$, the first method of calculation underestimates the effect of the lipid infusion; this explains why $G_{\text{non-Ox}}$ was not always significantly higher in other lipid-modified OGTTs (26, 37). Our result contrasts with reports that lipids inhibit glucose storage either evaluated indirectly, as we did, or more directly by measuring glycogen synthase activity on muscle biopsies (6) or by NMR (36). However, all these results were obtained during euglycemic clamp and not with a simultaneous increase in plasma glucose and insulin levels as in the present study. As discussed previously, the lack of inhibition of glucose nonoxidative disposal in our study cannot, contrary to other studies (23), be explained by an insufficient period of lipid infusion, since we infused lipids for 7 h. A glycogen-sparing effect of a lipid infusion has been described in animals (22) and suggested in humans (29). Our findings suggest that the slight lipid-induced increases in glucose and insulin levels divert glucose metabolism toward storage. This is consistent with the metabolic origin of insulin resistance proposed by Felber et al. (13).

It is of interest to compare the abnormalities in glucose tolerance induced by lipid infusion with those observed during starvation and in subjects with impaired glucose tolerance or NIDDM. Féry et al. (16) studied the mechanism of starvation diabetes by performing double-labeled OGTTs in normal subjects before and after 4 days of fast. The effect of starvation was similar to our observations with the lipid infusion, namely, higher residual SGP, lower glucose oxidation, and higher nonoxidative disposal. $R_{\text{ET}}$ was not affected by fasting, but the use of $[^{1-13}$C]glucose enabled correction for recycling, which was indeed slightly higher during fasting. Similar results have been reported by Mitrakou et al. (27) in “spontaneous” impaired glucose tolerance. The fate (oxidative or not) of utilized glucose was not reported in that study, but Felber et al. (12), using indirect calorimetry, found lowered values for oxidation but not for glucose nonoxidative disposal in obese subjects with impaired glucose tolerance. The results obtained in patients with NIDDM were different. In all cases (17, 18, 28), $R_{\text{ET}}$ and SGP were found elevated (although Féry et al. observed this only in severely hyperglycemic patients; Ref. 17), but $R_{\text{ET}}$ was not higher (at least after correction for glycosuria; Ref. 18). Glucose oxidation was lower (17), but there was also an impaired glucose nonoxidative disposal, as shown by similar (18) or even lower (28) values despite the hyperglycemia. This last abnormality cannot be explained by the effect of lipids, at least during acute administration.

In summary, a lipid infusion led to a moderate impairment in glucose tolerance in normal subjects. This was due to a defect in both the suppression of systemic glucose production and the stimulation of glucose oxidation. Infused glycerol contributed to the effect on systemic glucose production. The impairment in glucose oxidation is in accordance with Randle hypothesis. But this defect in glucose oxidation did not decrease insulin stimulated glucose disposal as initially proposed by Randle et al. (33) In fact, glucose intolerance was moderate because of a concomitant increase in glucose nonoxidative disposal. A further defect, concerning glucose nonoxidative disposal, therefore appears to be required for the development of NIDDM.

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