Stimulation of gluconeogenesis by intravenous lipids in preterm infants: response depends on fatty acid profile

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van Kempen, Anne A. M. W., Saskia N. van der Crabben, Mariët T. Ackermans, Erik Endert, Joke H. Kok, and Hans P. Sauerwein. Stimulation of gluconeogenesis by intravenous lipids in preterm infants: response depends on fatty acid profile. Am J Physiol Endocrinol Metab 290: E723–E730, 2006. First published November 15, 2005; doi:10.1152/ajpendo.00303.2005.—In preterm infants, both hypo- and hyperglycemia are a frequent problem. Intravenous lipids can affect glucose metabolism by stimulation of gluconeogenesis by providing glycerol, which is a gluconeogenic precursor, and/or free fatty acids (FFA), which are stimulants of the rate of gluconeogenesis. In 25 preterm infants, glucose production and gluconeogenesis were measured using stable isotope techniques during a 6-h infusion of glucose only, glucose plus glycerol, or glucose plus an intravenous lipid emulsion. Two lipid emulsions differing in FFA composition were used: Intralipid (~60% polyunsaturated FFA) and Clinoleic (~60% monounsaturated FFA). The rate of glucose infusion was 22 μmol·kg⁻¹·min⁻¹ in all groups. During the study infusion, the FFA concentrations were higher in both lipid groups vs. the glycerol group (P < 0.001). Compared with baseline, the glucose production rate increased in the Intralipid group, whereas it decreased in the other groups (P = 0.002) due to a significant increase in gluconeogenesis in the Intralipid group (P = 0.016). The plasma glucose concentration was significantly higher during Intralipid infusion vs. the other groups (P = 0.046). Our conclusion was that Intralipid enhanced glucose production by increasing gluconeogenesis in preterm infants. This can be ascribed to the stimulatory effect of FFA in addition to any effect of glycerol alone. The lack of stimulation of gluconeogenesis in the Clinoleic vs. the Intralipid group suggests that different classes of fatty acids exert different effects on glucose kinetics in preterm infants.

Because plasma FFA concentrations in preterm infants are much lower than in adults (18, 19, 49), the lack of FFA could be involved in restricted capacity for gluconeogenesis, predisposing these infants for hypoglycemia. On the other hand, very preterm infants routinely receive parenteral nutrition (including gradually increasing amounts of lipids) because enteral nutrition is not tolerated in sufficient amounts. Intravenous lipid emulsions contain FFA and could, therefore, play a role in the pathophysiology of hyperglycemia in preterm infants, a mechanism comparable with those described in adults with diabetes (11).

In healthy postabsorptive adults, FFA stimulate gluconeogenesis with a concomitant decrease in glycogenolysis, thereby maintaining the total glucose production at a constant rate (3, 10, 13, 16, 36, 46). In preterm infants, only three studies (12, 48, 55) have explored the effect of oral or intravenous lipid administration on glucose production in the first postnatal week, showing contradictory results. In the earliest study, administration of an intravenous lipid emulsion did not affect the glucose production rate, a finding that was comparable with those in adults. However, glucose production was already almost completely suppressed before the lipid infusion was started (55). The other two studies (12, 48) showed enhancement of glucose production in response to oral or intravenous lipid supply. In the latter study, gluconeogenesis was also measured, and it was revealed that both glucose production and gluconeogenesis were higher in the infants receiving lipids. Because intravenous lipid emulsions contain both FFA and glycerol, an important gluconeogenic precursor, the stimulating effect of the lipid emulsion could be caused solely by the glycerol component. Indeed, glycerol administration has been shown to increase gluconeogenesis in preterm infants (47). Conclusions about an additional effect of FFA on gluconeogenesis that are independent of the stimulatory effect of glycerol cannot be made because of important differences in the study design of these previous reports.

In addition to the stimulating effect of FFA on gluconeogenesis in general, the fatty acid composition could be important in the effect on glucose metabolism, although the published data are contradictory. In some studies (4, 15, 45, 52), saturated fatty acids show more potent effects on insulin release, glucose oxidation, glucose production, and gluconeogenesis than unsaturated fatty acids, although others (4, 8, 15, 45, 52) describe a greater effect from (mono)unsaturated than...
from saturated fatty acids on glucose stimulated insulin secretion.

The primary objective of our study was to measure the effect of an increase in plasma FFA concentration on gluconeogenesis [by mass isotopomer distribution analysis, (MIDA)] and endogenous glucose production (isotope dilution technique) in preterm infants by infusion of an intravenous lipid emulsion vs. glycerol administration or controls receiving only glucose. The fatty acid composition of the available intravenous lipid emulsions varies and depends on the lipid used as the base component. A secondary objective was to compare the effect of two intravenous lipid emulsions with a different fatty acid composition on glucose production and gluconeogenesis.

MATERIALS AND METHODS

Subjects. Preterm infants were recruited from the Neonatal Intensive Care Unit at the Emma Children’s Hospital, Academic Medical Center, Amsterdam, The Netherlands. Infants with a gestational age of $\leq 32$ completed weeks were eligible for the study. We included only infants with a postnatal age between 1 and 8 days, because the incidence of low plasma glucose concentrations is the highest in the first postnatal week. Exclusion criteria were severe hypoglycemia (for ethical considerations and necessity of high rates of glucose infusion), birth weight $< 10$th or $> 90$th percentile for gestational age (27), sepsis, perinatal depression (5-min APGAR score $< 7$), congenital malformations, severe respiratory distress, necessity of vasopressor support, and maternal diabetes or glucose intolerance. Written informed consent by the parents was obtained in all cases. This study was approved by the Medical Ethics Committee of the Academic Medical Center.

Study design. The study design is shown in Fig. 1. Before the study, all infants received enteral or parenteral nutrition (or a combination) in accordance with the nutrition protocol in our ward. Enteral and parenteral nutrition were discontinued 6 h before the study ($t = -9$ h) and replaced by intravenous glucose supply (unlabeled) at a rate of 33 $\mu$mol $\cdot$ kg$^{-1} \cdot$ min$^{-1}$ ($6$ mg $\cdot$ kg$^{-1} \cdot$ min$^{-1}$). The fluid intake was kept at the level prescribed by the attending clinician and was not changed during the study.

After obtaining a baseline blood sample at $t = -3$ h (8 AM) for determination of background isotopic abundance, a primed (272 $\mu$mol $\cdot$ kg body wt), continuous ([5.43 $\mu$mol $\cdot$ kg$^{-1} \cdot$ min$^{-1}$] $[-2.25$ $\mu$mol (glucose equivalents)$ \cdot$ kg$^{-1} \cdot$ min$^{-1}$]) infusion of [2-13C]glycerol (99% enriched; ARC Laboratories) was started at $t = -3$ h on top of the unlabeled glucose infusion to measure fractional gluconeogenesis. One infant (in the control group) received only [6,6-2H2]glucose.

In adults, adaptation to fasting is an established model for achieving a better understanding of the pathophysiology of metabolic processes. In preterm infants, prolonged fasting is not ethically acceptable because of the high risk of hypoglycemia. Therefore, we modified the fasting study design and measured glucose kinetics during a prolonged period of low-rate glucose infusion without administration of other macronutrients. Simultaneously with the start of the isotopic infusions, the rate of exogenous glucose infusion was diminished to 22 $\mu$mol $\cdot$ kg$^{-1} \cdot$ min$^{-1}$ ($4$ mg $\cdot$ kg$^{-1} \cdot$ min$^{-1}$) and maintained at this rate until the end of the study ($t = 6$ h). The glucose infusion rate of 22 $\mu$mol $\cdot$ kg$^{-1} \cdot$ min$^{-1}$ was chosen because, according to the present practice in our hospital, this rate is considered to be the lower limit of the required exogenous glucose supply in preterm infants for preventing plasma glucose concentrations of $< 2.5$ mmol/l. In addition to the glucose infusion, infants were randomly assigned to receive either intravenous glycerol [0.52 mg $\cdot$ kg$^{-1} \cdot$ min$^{-1}$ ($5.6$ $\mu$mol $\cdot$ kg$^{-1} \cdot$ min$^{-1}$)] or the intravenous lipid emulsion Intralipid [the standard intravenous lipid emulsion in our department (Fresenius Kabi Nederland, ’s-Hertogenbosch, The Netherlands)] or Clinolec (provided free of charge by Baxter, Utrecht, The Netherlands) during the last 6 h of the study; a control group received only glucose. The lipid emulsions were infused at a rate of 2.4 $\mu$mol $\cdot$ kg$^{-1} \cdot$ min$^{-1}$. The composition of the two lipid emulsions is shown in Table 1. Intralipid is based from soybean oil, and Clinolec is a mixture of olive oil and soybean oil (ratio of 4:1). Both lipid infusions resulted in glycerol supply at a rate of 0.52 $\mu$mol $\cdot$ kg$^{-1} \cdot$ min$^{-1}$ ($5.6$ $\mu$mol $\cdot$ kg$^{-1} \cdot$ min$^{-1}$; Table 1), which was similar to the glycerol group.

Infusions were administered through an intravenous (peripheral or central venous) catheter, which had been previously introduced for clinical reasons. Blood samples were drawn from a second intravenous catheter in the opposite limb or, if present, from an intra-arterial line.

After an equilibration period of 3 h of stable isotope infusion, blood samples were collected every hour (from $t = 0$ to 6 h) for the measurement of isotopic enrichments and plasma glucose concentration. At $t = 0, t = 3,$ and $t = 6$ h, blood was also collected for determination of FFA, triglyceride, and insulin concentrations.

Assays. All measurements were performed in duplicate, except for the MIDA samples, and all samples of individual newborns were analyzed in the same run.

Gas chromatography-mass spectrometry analyses were performed with a model 5890 Series II gas chromatograph, coupled with a model 5973 mass selective detector (Hewlett-Packard, Avondale, PA).

Fig. 1. Study design. Arrows indicate blood sampling times. Study infusion was either unlabeled glycerol, Intralipid, or Clinolec.
5,6-2H2 enrichment of glucose, which was assumed to be 350 ml/kg in preterm infants (Pharmacia Diagnostics, Uppsala, Sweden).

Clinical characteristics were calculated from the mass isotopomer distribution pattern of glucose, where F is [6,6-2H2]glucose infusion rate (in

\[ F = \frac{1}{V} \times \int_{0}^{t} ([E_2 - E_1] / (t_2 - t_1)) \times \int_{0}^{t} ([E_2 + E_1] / 2) \]

where \( V \) is [6,6-2H2]glucose infusion rate (in \( \mu \)mol \cdot kg\(^{-1}\) \cdot min\(^{-1}\)), \( E \) is the percentage of glucose molecules enriched with \(^2\)H in absolute values, \( C \) is plasma glucose concentration in (mmol/l), \( t \) = time at the sampling points (in min), and \( pV \) is the effective distribution volume of glucose, which was assumed to be 350 ml/kg in preterm infants (22). To calculate endogenous glucose production rate (GPR), exogenously infused glucose was subtracted from glucose rate. Precursor pool enrichment (p) and fractional gluconeogenesis (f) were calculated from the mass isotopomer distribution pattern of unlabeled and single- and double-labeled glucose derived from [2-\(^{13}\)C]glycerol, as described by Hellerstein and Neese (25) and Neese et al. (35). Absolute rate of gluconeogenesis was calculated as the product of \( f \times \text{glucose} R_0 \). Glycogenolysis was calculated by subtracting the rate of gluconeogenesis from GFR.

Statistics. Repeated-measures analysis of variance was used to investigate the changes in glucose kinetics and FFA, triglyceride, and insulin concentrations over time, and to compare these changes among the four groups (effect of protocol; mixed-model analysis of SPSS version 11.5.2), with time as a linear variable. To correct for potential differences due to differences at baseline (\( t = 0 \)), the difference of the variable with the value at \( t = 0 \) was included as the dependent variable in the analysis. The correlation between glucose production rate and plasma glucose concentration was also analyzed by the mixed-model analysis, with the glucose concentration as the dependent variable and the glucose production rate and study group as predictors. Unpaired data were analyzed by one-way analysis of variance. Statistical significance was set at \( P < 0.05 \).

RESULTS

Clinical data. The clinical characteristics of the infants are shown in Table 2. All infants were appropriate for gestational age. They were clinically stable, had normal body temperature, normal acid-base status, and normal oxygen saturation and \(^{13}\)CO2 concentrations. Five infants were ventilated with low ventilator settings and received morphine for sedation, consistent with the routines in our nursery. Seventeen infants required respiratory support by means of nasal continuous positive airway pressure. Most infants received antibiotics, but none had positive blood cultures or clinical signs of infection.

FFA concentrations. At baseline (\( t = 0 \)), FFA concentrations were low and comparable between the groups \((P = 0.338; \text{Table 3})\). During the study infusion (lipid emulsions or glycerol), the FFA concentrations were higher in both lipid groups vs. glycerol. There were no significant differences in the plasma FFA concentrations between the Intralipid and the Clinoleic group.

Glucose kinetics. At baseline \((t = 0)\), there were no significant differences between the groups in the parameters of glucose kinetics (Table 4). Because there were significant changes in some parameters of glucose kinetics during the study infusions, steady state could not be assumed, and non-steady-state equations were used. Changes during the 6-h study period in the four groups are shown in Table 4 and in Figs. 2, 3, and 4.

Table 1. Composition of intravenous lipid emulsions per 100 ml of emulsion

<table>
<thead>
<tr>
<th>Composition</th>
<th>Intralipid</th>
<th>Clinoleic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy, kcal</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Egg phospholipids, g</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Glycerol, g</td>
<td>4.24</td>
<td>4.24</td>
</tr>
<tr>
<td>Total</td>
<td>22.3</td>
<td>58.3</td>
</tr>
<tr>
<td>Oleic acid C18:1 n9</td>
<td>50.0</td>
<td>17.7</td>
</tr>
<tr>
<td>Arachidonic acid C20:4 n6</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>α-Linolenic acid C18:3 n3</td>
<td>6.99</td>
<td>2.0</td>
</tr>
<tr>
<td>Docosahexaenoic acid C22:6 n3</td>
<td>0.34</td>
<td>0.23</td>
</tr>
<tr>
<td>α-Tocopherol, mg</td>
<td>3</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Table 2. Clinical characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Respiratory Support and Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gestational age, wk</td>
</tr>
<tr>
<td>Control (n = 6)</td>
<td>30.0 ± 1.8</td>
</tr>
<tr>
<td>Glycerol (n = 6)</td>
<td>29.4 ± 1.6</td>
</tr>
<tr>
<td>Clinoleic (n = 7)</td>
<td>28.7 ± 1.6</td>
</tr>
<tr>
<td>Intralipid (n = 6)</td>
<td>29.3 ± 0.7</td>
</tr>
</tbody>
</table>

Data are means ± SD or number (n) of infants. There were no statistically significant differences in gestational age, birth weight, or postnatal age between the groups. nCPAP, nasal continuous positive airway pressure. Caffeine was administered in a maintenance dose of 2–3 mg/kg \(^{-1}\) \cdot \text{min}\(^{-1}\).
Glucose production rate significantly determined the plasma glucose concentration; estimate 0.04 (95% CI: 0.01, 0.06), P = 0.002. The study infusion had no influence on this effect (P = 0.632).

**Glycogenolysis and insulin concentrations.** Plasma triglyceride concentrations were determined only in the groups that received glycerol or a lipid emulsion. At baseline, the plasma triglyceride concentrations were comparable in these groups (P = 0.323; Table 3). During the study infusion (lipid emulsions or glycerol), the triglyceride concentrations were higher than in the glycerol group (Intralipid vs. glycerol, P = 0.027; Clinoleic vs. glycerol, P = 0.005). Differences between the Intralipid and the Clinoleic group were not statistically significant.

At baseline, the plasma insulin concentrations were comparable in all groups (P = 0.440; Table 3), and they did not change during the study period.

**DISCUSSION**

Our results showed that only the soybean oil-based intravenous lipid emulsion (Intralipid) enhanced glucose production was significantly higher during Intralipid infusion than in the control group (P = 0.042).

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by increasing gluconeogenesis and preventing a decrease in the rate of glycogenolysis over time in preterm infants during a low-dose glucose infusion. The increase in gluconeogenesis in the Intralipid group occurred concomitant with an increase in the total plasma FFA concentration. In the glycerol group, gluconeogenesis remained unchanged, indicating that the stimulatory effect in the Intralipid group was due to the FFA in this emulsion. The different responses of gluconeogenesis to the Intralipid and the Clinoleic infusions suggest that different classes of fatty acids exert different effects on glucose kinetics in preterm infants.

In the literature, several studies were published on the effect of lipid administration on glucose metabolism in newborn infants, consistently showing an increase in plasma glucose concentration (17, 24, 37–39, 40, 41, 51). Although data on the effect of lipids on glucose kinetics in newborn infants are scarce and contradictory (12, 48, 55), our results on the effect of the Intralipid emulsion on total glucose production are in line with two of these earlier studies (12, 48), but in contrast with data obtained in adults. In fact, lipid administration to healthy adults results in an increase in gluconeogenesis, but glucose production does not change due to a concomitant and reciprocal change in glycogenolysis (16, 36, 46). This mechanism is called hepatic autoregulation and is aimed at maintaining the rate of glucose production constant (34). In our preterm infants, the increase in gluconeogenesis during Intralipid infusion did not result in a decrease in glycogenolysis, and the glucose production rate reached a higher level than in the other groups. Explanations for this difference between preterm infants and adults could be that the mechanism of hepatic autoregulation is not yet present in preterm infants, or it is not active because hepatic glucose output does not completely cover glucose demands. The latter possibility could apply to our infants, because the total rate of glucose appearance was ~34 μmol·kg⁻¹·min⁻¹ during the study, which is ~75% of the amount necessary to completely suppress endogenous glucose production in preterm infants (26, 29).

The stimulating effect of Intralipid on gluconeogenesis could be due to the supply of either the gluconeogenic precursor glycerol or FFA. Previous studies (47) suggest that the ability of glycerol to increase gluconeogenesis approaches a maximum for a glycerol infusion rate of 5 μmol·kg⁻¹·min⁻¹.
Because of the use of [2-13C]glycerol at a rate of \(-4.5\ \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\), the maximum stimulation was probably already reached at baseline, before the start of the lipid or unlabeled glycerol infusion in our study. Additional supply of unlabeled glycerol did not result in a further increase of gluconeogenesis from baseline, in contrast with Intralipid infusion. Because both study groups received similar amounts of glycerol, the increase of gluconeogenesis in the Intralipid group must be ascribed to the stimulatory effect of certain fatty acids in addition to any effect of glycerol alone.

Several mechanisms by which FFA exert their effect on gluconeogenesis have been described. Hepatic FFA oxidation provides an important contribution to gluconeogenesis because this results in the production of NADH, acetyl-CoA, and ATP. These products contribute to the stimulation of gluconeogenesis: NADH produces reducing equivalents for gluconeogenesis, acetyl-CoA activates pyruvate carboxylase and increases citrate concentrations (which inhibit phosphofructokinase, thereby inhibiting glycolysis), and ATP provides energy for gluconeogenesis (53, 54). A second mechanism by which FFA stimulate gluconeogenesis could be by provoking insulin resistance. Insulin suppresses several enzymes that are involved in gluconeogenesis (7). In a situation of insulin resistance, the inhibiting effect on these enzymes is reduced and gluconeogenesis will persist. The rate-limiting site of this effect appears to be at the level of the interconversion between glucose 6-phosphate and glucose (30). Finally, FFA elevation can also directly affect gene expression and protein levels of the gluconeogenic enzymes pyruvate carboxylase, phosphoenolpyruvate carboxykinase, and glucose-6-phosphatase (5, 6, 33). As discussed above, infusion of different lipids had variable effects on glycogenolysis (3, 10, 13, 16, 36, 46). The mechanisms by which FFA influence glycogenolysis in healthy adults are not completely elucidated and could involve hepatic auto-regulation and hormonal changes (9, 10, 16, 30, 42). Changes in FFA concentrations induce changes in the plasma glucose and insulin concentrations, and both have been shown to affect glycogenolysis more than gluconeogenesis (14, 21). FFA oxidation competes with glucose breakdown in the glycolysis pathway and increases glucose 6-phosphate, an allosteric activator of glycogen synthesis and an inhibitor of glycogen breakdown (2, 23). Another possibility is that FFA exert a direct effect on glycogenolysis, but at the present time such mechanisms are unknown (14).

Intralipid and Clinoleic lipid emulsion differ primarily by their unsaturated fatty acid composition, and therefore our results suggest that different unsaturated fatty acids can have variable effects on glucose production in preterm infants. Other explanations would be 1) differences in the total concentrations of FFA between the Intralipid and Clinoleic groups, 2) differences in the glycerol concentrations, or 3) differences in the other components of the two lipid emulsions. However, the total FFA concentrations were comparable in the Intralipid and Clinoleic groups, the amount of glycerol was also similar, and the lipid emulsions we used exhibited little differences besides their unsaturated fatty acid content (Table 1). Clinoleic is an olive oil-based emulsion that contains predominantly monounsaturated fatty acids, whereas Intralipid is soybean oil based and contains mostly polyunsaturated fatty acids. Fatty acids can be classified in several ways, e.g., by degree of saturation or by omega class, etc. As a consequence, the difference in the fatty acid composition of the lipid emulsions we used can be expressed in different ways, and we cannot distinguish which class of unsaturated fatty acids is responsible for the effect on glucose metabolism.

It is generally recognized that different fatty acids could have different effects on glucose metabolism, but to our knowledge there are no studies comparing the effect of mono- vs. polyunsaturated fatty acids on glucose kinetics in humans. However, there is evidence from in vitro studies that mono- and polyunsaturated fatty acids could affect glucose metabolism in a different way (31, 32). To our knowledge, this is the first study to compare the effect of different lipid emulsions on glucose kinetics. However, there is accumulating evidence that different lipid emulsions have different immune modulating effects (28, 50).

Our data could have implications for clinical practice in preterm infants, specifically for the prevention and treatment of both hypo- and hyperglycemia. Hypoglycemia occurs mostly in the first days after birth, despite routine intravenous glucose supply. In this period, the other nutrients are usually prescribed in low amounts due to fluid restriction combined with the present clinical practice of gradually introducing (parenteral) nutrition. Our study shows the beneficial effect of the administration of the soybean oil-based lipid emulsion Intralipid on glucose production, which could be an argument for the early introduction of this intravenous lipid emulsion in preterm infants for the prevention or treatment of hypoglycemia. On the other hand, infants with hyperglycemia could benefit from the administration of parenteral nutrition containing a lipid emulsion with less effect on glucose production, such as Clinoleic, to combine sufficient energy supply with minimum effects on glucose metabolism.

Obviously, the use of different intravenous lipids to manipulate glucose metabolism in preterm infants needs to be evaluated in future studies. First, these studies should focus on further elucidation of the pathophysiological mechanisms of the interaction between glucose and lipid metabolism. Second, more information is needed on the metabolic fate of the intravenous lipid emulsions in the liver of the preterm infant, specifically lipid clearance, oxidation, and storage capability. The available data in preterm infants concern only lipid emulsions based on soybean oil and/or medium-chain triglycerides (43). Third, clinical outcomes must be studied in randomized, controlled trials, with the incidence of hypo- and hyperglycemia, growth, and psychomotor development as the main end points.

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REFERENCES


