Ascorbylperoxide Contaminating Parenteral Nutrition Perturbs the Lipid Metabolism in Newborn Guinea Pig

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ABSTRACT
The light exposure of parenteral nutritive solutions generates peroxides such as H$_2$O$_2$ and ascorbylperoxide [2,3-diketo-4-hydroxyperoxyl-5,6-dihydroxyhexanoic acid]. This absence of photoprotection is associated with higher plasma triacylglycerol (TG) concentration in premature infants and oxidative stress and H$_2$O$_2$-independent hepatic steatosis in animals. We hypothesized that ascorbylperoxide is the active agent leading to high TG. The aim was to investigate the role of ascorbylperoxide in glucose and lipid metabolism in an animal model of neonatal parenteral nutrition. Three-day-old guinea pigs received through a catheter in the jugular solutions containing dextrose plus 0, 90, 225, or 450 mg/kg (50% of the amount of ascorbylperoxide infused). After 4 days, blood and liver were sampled and treated for determinations of TG, cholesterol, markers of oxidative stress (redox potential of glutathione and F$_2$-isoprostane), and activities and protein levels of acetyl-CoA carboxylase (ACC), glucokinase, and phosphofructokinase (PFK). Ascorbylperoxide concentration was measured in urine on the last day. Data were compared by analysis of variance ($p < 0.05$). Plasma TG and cholesterol and hepatic PFK activity increased (200% of control), whereas ACC activity decreased (66% of control) in the function of the amount of ascorbylperoxide infused. Both markers of oxidative stress were higher in animals receiving the highest amounts of ascorbylperoxide. The logarithmic relations between urinary ascorbylperoxide and plasma TG ($r^2 = 0.69$) and hepatic PFK activity ($r^2 = 0.26$) were positive, whereas they were negative with ACC activity ($r^2 = 0.50$). In conclusion, ascorbylperoxide contaminating parenteral nutrition stimulates glycosis, allowing higher availability of substrates for lipid synthesis. The logarithmic relation between urinary ascorbylperoxide and plasma TG suggests a very low efficient concentration.

Intravenous nutritive support is essential for those who cannot be fed by mouth. This mode of nutrition is frequent in premature infants born before 28 weeks of gestation in whom the gastrointestinal tract is immature. Parenteral nutritive solutions are compounded to provide all essential nutrients the main source of peroxides is the multivitamins' moiety of parenteral nutritive solution (Lavoie et al., 1997). The photoexcited riboflavin catalyzes the electron transfer to dissolved oxygen to produce superoxide anion and singlet oxygen, which react with electron donors such as lipid, amino acids, and ascorbate to generate peroxide (Helbock et al., 1993; Lavoie et al., 1997; Laborie et al., 1998; Knafo et al., 2005). Eighty percent of these peroxides are H$_2$O$_2$ (Lavoie et al., 1997).

In infants, the absence of photoprotection of parenteral nutrition is associated with a higher concentration of peroxide in urine (Laborie et al., 2000), glucose in blood, and triacylglycerol (TG) in plasma (Khashu et al., 2009). These observations were prevented by light protection from the preparation of the nutritive solution to the delivery to the infants. In animals, photoexposed parenteral nutrition induced oxidative stress (Lavoie et al., 2000; Chessex et al., 2001) and hepatic steatosis (Chessex et al., 2002). Because
Ascorbylperoxide on Glycolysis and Lipogenesis

Materials and Methods

Ascorbylperoxide and filtered against a 30-kDa filter Centricon Plus-20.

A solution containing 1.8 mM arsenazo III (sodium salt) in 2.5 mM sodium azide (Sigma-Aldrich) was used to prepare the final solutions containing 0.05, 0.1 mM ascorbylperoxide. The infused solutions were replaced each day by new freshly prepared solutions.

Analytical Measurements

**Ascorbylperoxide.** Based on previous study (Knafo et al., 2005), ascorbylperoxide in infused solution and urine was quantified by using an Agilent Technologies (Santa Clara, CA) LC/MS 1100 mass spectrometer and 1-2-oxy-thiazolidine 4-carboxylic acid (OTC) (Aldrich Chemical Co., Milwaukee, WI), as an internal standard. The linear correlations demonstrated the absence of interaction between OTC and ascorbylperoxide into the assay. The stability of OTC was not affected by the pH (2–9) or freezing at −20°C (until 168 days). Ascorbylperoxide concentration at −80°C decreases in function of time (y = 0.30%·d−1·x + 100%; r2 = 0.83).

**Glutathione.** Immediately after sampling, 0.5 g of liver was homogenized (2 × 10 s with Polytron Teador; Biospec Products Inc, Dremel-Racine, WI) in 2.5 ml of iced and freshly prepared 5% (w/v) metaphosphoric acid and centrifuged for 3 min at 7200g. Pellets and supernatants were kept at −80°C until protein and glutathione determinations, respectively. GSH and GSSG were quantified by capillary (75-μm × 50-cm silica) electrophoresis (75 mM boric acid and 25 mM Bis-Tris, pH 8.4, 28°C, 18 kV) as described previously (Lavoie et al., 2008, Turcot et al., 2009). The redox potential refers here to the half-cell reduction potential of the GSSG (2H+/H2S) as calculated by using the Nernst equation (25°C, pH 7.0) (Schäfer and Buettner, 2001).

**S-Isoprostane F2α, Triacylglycerol, Total Cholesterol, Blood Glucose.** Isoprostane levels were determined by using a commercial enzyme immunoassay kit (Cayman Chemical, Ann Arbor, MI) as reported previously (Chessex et al., 2002). Triacylglycerol and total cholesterol were measured by using an enzymatic colorimetric test from Roche Diagnostics (Indianapolis, IN) (Turcot et al., 2009). Blood glucose was quantified with the OneTouch Ultra glucometer (Johnson & Johnson, New Brunswick, NJ).

**Acetyl-CoA Carboxylase Activity.** ACC activity was measured on the 6% PEG 8000 (Sigma-Aldrich, St. Louis, MO) fraction (Kudo et al., 1995) as reported previously (Turcot et al., 2009). The measurement was based on the addition of carbon atom from 14C bicarbonate (NaH14CO3; 14 mM/cm; Sigma-Aldrich) on acetyl-CoA and was expressed as nmol malonyl-CoA produced/min/mg protein. The assay was performed after preincubation in the presence or not of 7.5 mM glutamate, which revealed the total activity of the enzyme by stimulating phosphatase protein 2A (Gaussin et al., 1996).

**Glucokinase Activity.** The activity was determined according to the method described by Perre et al. (1996) and Xu et al. (2004). In brief, glucokinase (GK) was measured spectrophotometrically on 23,000g supernatant of liver homogenate in a system coupled with glucose-6-phosphate dehydrogenase after a 20-min incubation at 30°C.
37°C. Difference in activities obtained by using 100 and 0.5 mM glucose as substrate corresponds to the glucokinase activity.

**Phosphofructokinase-1 Activity.** The activity was determined according to the method of Hamer and Dickson (1987) and Karakash et al. (1977). In brief, PFK-1 was assayed by the measurement of NA DH oxidation at 340 nm on 100,000g supernatant of liver homogenate in a system coupled with aldolase, triose phosphate isomerase, and α-glycero phosphohydroxide dehydrogenase.

**Western Blots: Phosphofructokinase and Glucokinase.** According to the method of Abnous and Storey (2008) and Rideau et al. (2008), 300 mg of liver was homogenized in 0.6 ml of buffer (pH 7.4) containing 10 mM Tris, 1 mM EDTA, 1 mM EGTA, 150 mM NaCl, 100 mM NaF, 2 mM orthovanadate sodium, 1% (v/v) Triton X-100, 0.01% (v/v) 10% SDS, 2 mM phenylmethylsulfonyl fluoride, and protease inhibitor cocktail (one complete tablet/20 ml; Roche Diagnostics). After 1-h incubation at 4°C, the suspension was centrifuged (4°C) 30 min at 6300g. The supernatant was centrifuged (4°C) for 45 min at 18,000g. Fifty micrograms from supernatant was separated on 8% polyacrylamide electrophoresis (100 V, 90 min) and electroblotted onto polyvinylidene difluoride membrane (90 V, 2 h at 4°C). The membrane was incubated overnight at 4°C with the first antibody [polyclonal anti-human GK (Abnova Corporation, Taipei, Taiwan) (1:1000), and monoclonal anti-mouse vinculin (Abnova Corporation) (1:2500) and 1 h with the second antibody [goat anti-mouse IgG-horseradish peroxidase secondary antibody (RRD Systems, Minneapolis, MN) (1:5000)]. After washing (4 × 15 min), the second antibody was revealed by chemiluminescence (25% SuperSignal West Femto; 75% SuperSignal West Pico; Pierce Biotechnology, Rockford, IL) on X-ray film. The quantification was done by densitometry (Fluor Chem 8800 imaging system; Packard Biotechnology Company, Meriden, CT).

**Western Blot: Acetyl-CoA Carboxylase.** According to the method of Ouadda et al. (2009), 50 mg of frozen liver was homogenized in 0.5 ml of buffer (pH 7.5) containing 50 mM HEPES, 150 mM NaCl, 1.5 mM MgCl2, 1 mM EGTA, 1% (v/v) Triton 100-X, 50 mM NaF, 10% glycerol, 1 mM phenylmethylsulfonyl fluoride, 5 μg/ml aprotinin, 5 μg/ml leupeptin, and 1 mM Na3VO4. After centrifugation (13,000 rpm, 20 min, 4°C), 25 μg of protein from supernatant was separated on 8% polyacrylamide electrophoresis (170 V, 50 min), electroblotted onto polyvinylidene difluoride membrane (100 V, 70 min at 4°C), and blocked (1 h at room temperature) with skimmed milk at 5% in phosphate-buffered saline–Tween 20. The membranes were incubated overnight at 4°C with the polyclonal anti-human ACC (Cell Signaling Technology, Danvers, MA) (1:500) and the monoclonal anti-mouse vinculin (Abnova Corporation) (1:2500) followed by 1-h incubation with goat anti-rabbit IgG-horseradish peroxidase secondary antibody (Promega, Madison, WI) (1:20,000). After four washes (15 min), the result was revealed by chemiluminescence (100% Western Lightning Chemiluminescence Reagent, PerkinElmer Life and Analytical Sciences, Waltham, MA) on X-ray film. The quantification was done by densitometry (Fluor Chem 8800 imaging system).

**Statistical Analysis.** Data were presented as mean ± S.E.M. and compared by analysis of variance after validation of homoscedasticity using Bartlett’s χ2 test. Logarithmic transformation of GSH, GSSG, and ACC Western blot data was used to meet homoscedasticity. The orthogonal comparisons used were [(0 versus 1 μmol/day ascorbylperoxide group) versus 4 μmol/day] versus 7 μmol/day) to statistically document the lowest efficient concentration of ascorbylperoxide. The level of significance was set at p < 0.05.

**Results**

The initial body weight (106 ± 3 g), final body weight (100 ± 2 g), and liver weight (3.6 ± 0.1 g or 37.0 ± 1.8 mg/g of body weight) did not differ between groups (F1,23 < 3.9). Blood glucose was similar (F1,19 < 2.3) between groups (8.0 ± 0.4 mM).

**Table 1**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Infused</th>
<th>Urine</th>
<th>Urine</th>
<th>Urine/Infused</th>
</tr>
</thead>
<tbody>
<tr>
<td>μmol/day</td>
<td>μmol/mg</td>
<td>μmol/ml</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1,17 &lt; 9.1</td>
<td>0.6 ± 0.1</td>
<td>0.04 ± 0.01</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>F1,17 &lt; 9.1</td>
<td>1.1 ± 0.1</td>
<td>1.5 ± 0.3</td>
<td>0.15 ± 0.03</td>
<td>53 ± 10</td>
</tr>
<tr>
<td>F1,17 &lt; 9.1</td>
<td>4.0 ± 0.1</td>
<td>3.2 ± 0.7</td>
<td>0.30 ± 0.01</td>
<td>82 ± 7</td>
</tr>
<tr>
<td>F1,17 &lt; 9.1</td>
<td>7.0 ± 0.2</td>
<td>6.7 ± 0.8</td>
<td>0.43 ± 0.05</td>
<td>87 ± 1</td>
</tr>
</tbody>
</table>

* Ascorbylperoxide infused = mean of 3 days.

† Urine from last day.

‡ Ratio obtained after deduction of endogenous content (95% confidence value from group without infusion of ascorbylperoxide = 0.80 μmol/mg creatinine or 54 μM).

The exact amounts of ascorbylperoxide received by animals are reported in Table 1 and used in the figures to qualify the four groups. Data show that ascorbylperoxide is eliminated in urine. The concentration measured in urine from animals that were not infused with ascorbylperoxide suggests an endogenous generation of this molecule. The threshold of this endogenous value (95% confidence) was 0.80 μmol/mg creatinine or 54 μM. By deducting this limit to urinary concentration of ascorbylperoxide, the calculated recovery in urine increased in the function of the infused amount and reached a plateau of more than 80% with the infusion of 4 μmol/day (Table 1).

To challenge the hypothesis of the impact of ascorbylperoxide on TG, the experimental design allowed us to investigate two options: modification of fatty acids synthesis, characterized here by the ACC activity, and modification of the substrate availability from glycolysis, characterized by GK and PFK activities, to sustain the lipid synthesis. The determination of TG and total cholesterol allowed us to distinguish between the two options. Indeed, a modification in TG alone would suggest an effect of ascorbylperoxide on fatty acid synthesis, whereas a similar modification of both lipids would suggest an impact on a common substrate. Figure 1 shows that both TG (A) and total cholesterol (C) were increased in the plasma of animals infused with ascorbylperoxide. The difference was significant with the infusion of 4 μmol/day for plasma TG (F1,17 = 9.1) and 1 μmol/day for plasma total cholesterol (F1,17 = 9.6). No effect of ascorbylperoxide was observed in liver for TG (F1,17 < 1.9) (Fig. 1B) or total cholesterol (F1,17 < 0.2) (Fig. 1D).

ACC exists in its active and inactive (phosphorylated) form. The basal activity (nonphosphorylated form) of ACC (Fig. 2A) was negatively affected by infused ascorbylperoxide or total cholesterol (Fig. 2B) was lower in animals infused with at least 4 μmol/day of ascorbylperoxide (F1,17 = 7.4), whereas the ratio of the activities (Fig. 2C) was already affected with the lowest amount of ascorbylperoxide infused (F1,17 = 9.2), suggesting that ascorbylperoxide induces a dephosphorylation of the enzyme. The activation of ACC by ascorbylperoxide has already been reported in our animal model (Knafo et al., 2005). On the other hand, Western blot analysis (Fig. 2D)
Ascorbylperoxide infused (µmol/d)

![Graph A](image1)

![Graph B](image2)

![Graph C](image3)

![Graph D](image4)

Fig. 1. Plasma and hepatic triacylglycerol and cholesterol levels in the function of an infused amount of ascorbylperoxide. A and B, triacylglycerol concentration in plasma (A) was significantly higher in animals infused with at least 4 µmol of ascorbylperoxide per day, whereas there was no difference in triacylglycerol between groups in liver (B). C and D, total cholesterol concentration in plasma (C) was significantly higher in animals infused with at least 1 µmol ascorbylperoxide per day, whereas there was no difference in cholesterol between groups in liver (D). Results are expressed as mean ± S.E.M. (n = 4–7). *, p < 0.05; **, p < 0.01.

Ascorbylperoxide infused (µmol/d)

![Graph E](image5)

![Graph F](image6)

Fig. 2. Hepatic acetyl-CoA carboxylase in the function of an infused amount of ascorbylperoxide. In the function of an increased amount of ascorbylperoxide infused, the basal (A) and the total activity (B) of ACC decreased, and the ratio of the basal on the total activity (C), reflecting the proportion of unphosphorylated and active form of the enzyme, increased, whereas the relative protein amount (D) decreased. Vinculin abundance did not vary statistically between groups. Results are expressed as mean ± S.E.M. (n = 4–7). *, p < 0.05; **, p < 0.01.

shows that the protein level of ACC was lower in animals infused with ascorbylperoxide (F₁,₁₉ = 6.2). Together, these data suggest that ascorbylperoxide has induced a more active (less phosphorylated) ACC but in a lower protein amount, whose resultant was a weaker activity.

The second option that can explain increased lipid production was a greater availability of substrate. Acetyl-CoA, which can derive from glycolysis, is a common substrate for the synthesis of TG and cholesterol. Glycokinase is the key enzyme in liver to favor the glucose uptake by hepatocytes (Agius, 2008), whereas PFK-1 is the enzyme limiting the entry of glucose in glycolysis, leading to formation of acetyl-CoA. GK activity (Fig. 3A) decreased (F₁,₁₉ = 4.7) in animals infused with the highest amount of ascorbylperoxide (7 µmol/day), whereas 4 µmol/day was sufficient to induce a rise in PFK activity (F₁,₁₉ = 9.1) (Fig. 3B). The protein amount of both enzymes did not vary between groups (F₁,₁₉ < 0.6) (Fig. 3 C and D). Plasma TG was not explained by PFK activity (linear correlation r² = 0.13), whereas it correlated significantly and negatively with ACC activity (y = −7.6 nmol·min⁻¹·mg protein⁻¹·mM⁻¹·x + 6.8 mM, r² = 0.37, p < 0.01) (Fig. 4).

The hepatic oxidative effect of ascorbylperoxide (Fig. 5) has been revealed with the highest amount infused (7 µmol/day). Indeed, in this group, isoprostane level (Fig. 5B) and the redox potential of glutathione (Fig. 5A) were higher (F₁,₁₉ > 6.7). The more oxidized status of glutathione in this group
was associated with a lower tissue concentration of GSH \((F_{1.10} = 5.6)\) (Table 2) rather than a modification in GSSG level \(F_{1.10} < 3.8\).

Figure 6 shows TG values (A) and the activities of PFK (B) and ACC (C) in the function of urinary concentration of ascorbylperoxide. TG value and PFK activity increased positively in a logarithmic function with ascorbylperoxide \(\text{TG: } y = 0.063\ln(x) + 0.20 \text{ mM}, \ r^2 = 0.69, p < 0.01; \text{ PFK: } y = 1.11\ln(x) + 5.7 \text{ nmol \cdot min}^{-1} \cdot \text{ mg protein}^{-1}, \ r^2 = 0.26, p < 0.05.\) In contrast, the logarithmic relation between ACC activity and urinary ascorbylperoxide was negative \(y = -0.71\ln(x) + 5.4 \text{ nmol \cdot min}^{-1} \cdot \text{ mg protein}^{-1}, \ r^2 = 0.50, p < 0.01.\)

### Discussion

An important finding of the study is that infusion of an increasing amount of ascorbylperoxide is associated with a rise of plasma triacylglycerol and cholesterol concentrations and stimulation of PFK activity. In contrast to what was expected, these effects do not seem to occur through oxidative stress caused by this peroxide. Indeed, in a concentration range affecting TG and PFK, two markers of oxidative stress, isoprostane and redox potential of glutathione, were affected only by the infusion with the highest concentration of ascorbylperoxide. More surprising was the drop of ACC activity in the function of infused ascorbylperoxide. This last effect supports the notion that ascorbylperoxide induces the production of TG by improving substrate availability deriving from glycolysis rather than by stimulation of enzymatic machinery of lipogenesis. This notion can explain the fact that levels of both TG and cholesterol were increased.

The opposite effect on PFK and ACC activities could be explained by multiple actions of ascorbylperoxide such as on the allosteric modulation by different molecules or by an upstream common effect such as on insulin. This last possibility seems to be more appropriate because it is more probable that ascorbylperoxide acts on only one system. For instance, insulin is known to stimulate PFK activity by phosphorylation (Müller et al., 1988), whereas it activates ACC by dephosphorylation (Witters et al., 1988) or by stimulating its gene transcription through sterol regulatory element-binding protein 1 (Tong, 2005). Hence, the insulin-mimic effect of ascorbylperoxide can explain our results on PFK and ACC activation (Fig. 3C). The loss of activity and protein level of ACC in animals infused with ascorbylperoxide can be explained by a negative feedback effect of newly synthesized fatty acids on the expression of sterol regulatory element-binding protein 1 (Field et al., 2002). This last suggestion is supported by the negative correlation between ACC activity and plasma TG (Fig. 4). On the other hand, it is not excluded that ascorbylperoxide can perturb the clearance of plasma lipids; this possibility was not an aim of the present study. The relation between ascorbylperoxide, insulin, and clearance should be investigated in a further study in which all constituents of parenteral nutrition could be present to mimic more closely the clinical situation. Indeed, the generation of ascorbylperoxide in vitro is affected by the presence of other compounds: 1% multivitamin preparation in solution containing only dextrose (8%) generates 150 ± 11 µM ascor-
Ascorbylperoxide, whereas the same concentration of multivitamin but in a completed parenteral nutritive solution, including amino acids and lipids, produces a ascorbylperoxide concentration of 36 ± 1 µM (J. C. Lavoie, personal communication). The relationship between infused ascorbylperoxide and its concentration in urine is strong (Table 1). The high ratio of the urinary concentration on the quantity infused suggests that infused ascorbylperoxide is easily eliminated in urine. The study of the relationship (Fig. 6) between urinary concentration of ascorbylperoxide and plasma TG and hepatic activity of PFK and ACC suggests that an efficient threshold did not exist for this molecule. The fact that ascorbylperoxide is detectable in urine of animals that were not infused with the molecule suggests an endogenous formation, which was also observed in our previous study (Knafo et al., 2005). The values of the endogenous threshold (0.8 µmol/mg creatinine) correspond to the inflection point of the curves shown in Fig. 6 (vertical dashed line). Therefore, a little addition of ascorbylperoxide could have metabolic consequences.

The premise of the study was to explain the clinical observation done in premature infants that the absence of adequate photoprotection of parenteral nutrition was associated with a higher plasma TG compared with those receiving light-protected parenteral nutritive solution (Khashu et al.,

Table 2

<table>
<thead>
<tr>
<th>Ascorbylperoxide Infused (µmol/day)</th>
<th>0</th>
<th>1.1 ± 0.1</th>
<th>4.0 ± 0.1</th>
<th>7.0 ± 0.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSH (nmol/mg protein)</td>
<td>35 ± 5</td>
<td>82 ± 23</td>
<td>33 ± 13</td>
<td>19 ± 8*</td>
</tr>
<tr>
<td>GSSG (nmol/mg protein)</td>
<td>0.35 ± 0.03</td>
<td>1.02 ± 0.29*</td>
<td>0.37 ± 0.10</td>
<td>0.26 ± 0.06</td>
</tr>
<tr>
<td>GSSG/total glutathione (%)</td>
<td>2.2 ± 0.4</td>
<td>2.9 ± 0.6</td>
<td>3.0 ± 0.9</td>
<td>3.5 ± 1.1</td>
</tr>
</tbody>
</table>

Fig. 5. Hepatic markers of oxidative stress in the function of an infused amount of ascorbylperoxide. Redox potential of glutathione (A) and the level of isoprostane (B) were higher in animals infused with the highest amount of ascorbylperoxide. Results are expressed as mean ± S.E.M. (n = 4–7). *p < 0.05; **, p < 0.01.

Fig. 6. Plasma triacylglycerol concentration, hepatic phosphofructokinase, and acetyl-CoA carboxylase activities in the function of urinary triacylglycerol concentration. A and B, triacylglycerol concentration in plasma (A) and PFK activity (B) increased positively in a logarithmic function with ascorbylperoxide in urine [TG: y = 0.063ln(x) + 0.20 mM, r² = 0.69, p < 0.01; PFK: y = 1.1ln(x) + 5.7 nmol·min⁻¹·mg protein⁻¹, r² = 0.26, p < 0.05]. C, in contrast, the logarithmic relation between ACC activity and urinary ascorbylperoxide was negative [y = −0.7ln(x) + 5.4 nmol·min⁻¹·mg protein⁻¹, r² = 0.50, p < 0.01]. The dashed line represents the calculated threshold limit of endogenous generation of ascorbylperoxide in urine.


development.
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2009). Because the light exposure of parenteral nutritive solution favors the generation of ascorbylperoxide (Lavoie et al., 2004; Knafo et al., 2005), the present study suggests that the active agent coming from parenteral nutrition is ascorbylperoxide, which induces a metabolic phenotype similar to an antenatal profile of the metabolism of glucose and lipids. Indeed, during the antenatal period, the activity of PFK is higher (Casado et al., 1996) and that of ACC is lower (Walther and Batenburg, 1995) than those after birth. The consequences of maintaining such metabolism are unknown. However, because ascorbylperoxide is derived from ascorbate, a vitamin largely available, additional studies are needed to assess the biological or toxic role of this compound in the human population.

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Photooxidation of parenteral multivitamins induces hepatic steatosis in a neonatal
levels or cAMP-stimulated protein kinase activity ratios. Biochim
Biophys Acta 1245:283–292.
peroxide generation.

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