Neonatal Exposure to Oxidants Induces Later in Life a Metabolic Response Associated to a Phenotype of Energy Deficiency in an Animal Model of Total Parenteral Nutrition

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ABSTRACT: Failure to protect total parenteral nutrition (TPN) from ambient light exacerbates the generation of peroxides, which affects blood glucose and plasma triacylglyceride (TG) in neonates. Based on the concept that the origin of adult diseases can be traced back to perinatal life, it was hypothesized that neonatal exposure to peroxides may affect energy availability later in life. Three-day-old guinea pigs, fitted with a jugular catheter, were fed regular chow (sham) $\pm$ i.v. 350 μ M H₂O₂ (sham + H₂O₂) or nourished with light-protected TPN [TPN(–)L, 209 $\pm$ 9 μ M peroxides] or light-exposed TPN [TPN(+)L, 365 $\pm$ 15 μ M peroxides]. After 4 d, infusions were stopped and animals fed chow. Spontaneous ambulatory movements, fasting blood glucose, glucose tolerance, TG, hepatic activities of glucokinase, phosphofructokinase (key enzymes of glycolysis), and acetyl-CoA carboxylase (key enzymes of lipogenesis) were determined at 12–14 wk and compared by ANOVA ($p < 0.05$). Relative to sham, the animals from sham + H₂O₂, TPN(–)L and TPN(+)L groups had lower plasma TG explained for 36% by low phosphofructokinase activity; they had lower glucose tolerance, lower body weight, and lower physical activity. In conclusion, neonatal exposure to oxidant molecules such as peroxides has important consequences later in life on lipid and glucose metabolism leading to a phenotype of energy deficiency. (*Pediatr Res* 68: 188–192, 2010)

The association between oxidative stress and characteristic features of the metabolic syndrome, such as diabetes, hypertension, and dyslipidemia, is well documented (1–6). Human (7) and animal studies (8,9) suggest that the origin of the metabolic syndrome can be traced back to perinatal life, a time when newborn infants are at greater risk of oxidative stress caused by weak antioxidant defenses (10–12) or exposure to an oxidative environment or both (13–18). Several reports suggest that, in neonates, oxidative stress triggers the events that lead to programming of adult diseases (19–22).

Total parenteral nutrition (TPN) represents a source of oxidants in the form of peroxides that can be calibrated either by applying or not photoprotecting. The peroxides are derived from interactions between dissolved oxygen and electron donors such as lipid, amino acid, or ascorbic acid (23,24). The

reaction is catalyzed by photoexcited riboflavin (24). Therefore, the main active agents participating in the generation of peroxides in TPN are ambient light [(+)L] and multivitamin preparations (MVP) (23,24). Photoprotection [(–)L] of TPN reduces the levels of peroxides by close to 50% (23,25,26). Absence of photoprotection of TPN is associated in preterm newborn infants with higher urinary peroxide concentrations (16), higher blood pressure in girl babies (15), and greater blood glucose and plasma triacylglycerol concentrations (13). Hence, peroxides contaminating TPN solutions are not completely quenched by newborns infants and are thought to be an agent initiating metabolic perturbations. We questioned whether these peroxides are linked to metabolic consequences later in life.

Based on the concept that neonatal oxidative stress may interfere with metabolic programming (27), we hypothesized that neonatal exposure to peroxides such as those generated in solutions of parenteral nutrition, induces a permanent modification in lipid and glucose metabolism especially lipogenesis and/or glycolysis. Perturbations in lipid and glucose metabolism, which are fuels for energy production, could have long-term consequences on growth and physical activity, thereby affecting global development. The aim of this study was to measure in adult guinea pigs metabolic responses and spontaneous physical activity after a brief neonatal exposure to i.v. oxidant molecules limited to the first wk of life. A second objective was to assess if these modifications were related to the infusion of peroxides.

MATERIALS AND METHODS

Experimental design. The metabolic response and the levels of physical activity were compared in four groups of animals. The experiments were designed to test whether the effect of light-exposed TPN was associated to hydrogen peroxide contaminating i.v. nutritional solutions. Each one of the 3-d-old male guinea pig pups (Charles River, St-Constant, Quebec, Canada) had a catheter secured in the right jugular vein (28–32) for the entire duration of the study. Animals were randomly assigned to receive one of the following regimens for 4 d between d 3 and 7 of life:

Abbreviations: ACC, acetyl-CoA carboxylase-1 EC2.7.1.12; GK, glucokinase (hexokinase IV) EC2.7.1.2; PFK, phosphofructokinase-1 EC2.7.1.11.; TG, plasma triacylglycerol concentration; TPN, total parenteral nutrition; TPN(–)light, light-protected TPN; TPN(+)light, light-exposed TPN

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Sham: Animals fed exclusively by mouth (while catheter *in situ*) with regular chow for guinea pig (185 ± 25 kcal/kg/d; control group).

Sham + H₂O₂: Sham animals receiving i.v. a solution containing 350 μ M H₂O₂ + 0.9% (wt, vol) NaCl + 1 U/mL heparin but fed by mouth regular chow *ad libitum*. The peroxide concentration corresponds to the level received in the TPN(+)-L group.

TPN(+)-L: Animals fed exclusively with TPN (no enteral feeding) [5.4 g/kg/d amino acids (Travasol; Baxter, Mississauga, Ontario, Canada), 3.8 g/kg/d lipids (Intralipid 20%; Pharmacia Upjohn, Baie d'Urfé, Quebec, Canada), 8% (wt, vol) dextrose, 1 U/mL heparin, electrolytes, and 1% MVP (Multi-12 pediatric; Sandoz, Montréal, Quebec, Canada) = 124 ± 25 kcal/kg/d]. The i.v. solution remained without photoprotection and contained 365 ± 15 μ M. The level of light exposure was 75–feet candles.

TPN(-)-L: Animals fed exclusively with TPN (solution as above) protected from light (-)L, corresponding to a peroxide concentration of 209 ± 9 μ M.

The i.v. solutions (H₂O₂ and TPN) were infused continuously *via* the jugular catheter at 220 mL/kg/d and changed daily. After 4 d of treatment, at 1 wk of age, i.v. infusion was stopped, and catheters were closed by a node on its external port. Animals had free access to regular chow and water until the end of the study 13 wk later. During the first 2 d on regular chow (sham and TPN groups), solid food (pellet) was humidified to ensure that animals were actually feeding. Body weight was monitored each month.

During their 12th wk of age, physical activity was measured as counts of spontaneous ambulatory activity using an infrared movement detector placed in the animal cage (Digiscan DMicro Monitor; Accuscan Instruments, Inc., Columbus, OH). One count corresponds to each interruption of the infrared beam by animals (Versamax Analyser; Accuscan Instruments). Counts were registered during 2 h (between 12 and 14 h) after 1 h of stabilization.

At 13 wk, blood glucose was measured after 12 h fasting with OneTouch Ultra glucometer (Johnson & Johnson). For the glucose tolerance test (GTT), blood glucose was determined immediately before and every 30 min after an i.p. injection of 2 mL of 50% dextrose solution/kg body weight, for a total of 150 min.

At 14 wk, after 12 h of fasting, blood was collected in K₃EDTA-coated tubes. After centrifugation ($3300 \times g$, 4 min at room temperature), plasma was stored at -80°C . The liver was removed, rinsed in 0.9% NaCl, rapidly minced, aliquoted, and stored at -80°C . Plasma triacylglyceride (TG), hepatic TG, and activities of glucokinase (GK), phosphofructokinase (PFK), and acetyl-CoA carboxylase (ACC) were determined.

Animals were housed in the animal facility with constant temperature and 12/12-h light/dark cycle. This study was approved by the Institutional Review Board for the care and handling of animals, in accordance with guidelines of the Canadian Council of Animal Care.

Analytical procedures. Peroxide concentrations in i.v. solutions were determined using ferrous oxidation-xylenol orange assay that measures a wide range of hydroperoxides (23). Triacylglycerol concentrations were determined on plasma and liver after Folch extraction using a colorimetric commercial kit (Roche Diagnostics, Laval, Quebec, Canada) (9). Hepatic ACC activity was determined as an index of the synthetic activity for lipogenesis. ACC activity was measured from 6% PEG 8000 (Sigma Chemical-Aldrich) fraction, as previously reported (9,33), and was expressed as nanomoles of malonyl-CoA produced per minute per milligram of protein (U). Hepatic GK activity (34,35) was determined as the first key step enabling glucose to enter glycolysis. The GK activity was obtained by subtracting the activity measured using high glucose concentration (100 mM; total activity) from those measured with low concentration (0.5 mM; hexokinase activity). The activity expressed as nanomoles per minute per milligram of protein (U). Hepatic PFK activity (36,37) was determined as the enzyme allowing glucose-6-phosphate to be processed through glycolysis to produce ATP and pyruvate, the precursor of acetyl-CoA. PFK activity was measured on the cytosolic fraction ($100,000 \times g$ supernatant, 10 min, and 4°C) and was expressed as nanomoles per minute per milligram of protein (U).

Statistical analysis. Results were expressed as mean $\pm$ SEM and compared by ANOVA. The null hypothesis was defined as peroxides and mode of nutrition (enteral *versus* parenteral) having no long-term metabolic modifications. All comparisons were orthogonal. When necessary, natural logarithm transformation was used to achieve homoscedasticity (Bartlett's χ^2 test). The level of significance was set at $p \leq 0.05$.

RESULTS

Biochemical phenotype. Plasma TG concentrations (Fig. 1A) were lower ($F_{1,24} = 11.3$) in animals that received i.v. oxidant molecules [H₂O₂ or TPN(+)-L] during their first wk of

Figure 1. Concentration of triacylglycerol in plasma and liver at 14 wk of age. Sham: control animals fed with regular chow; sham + H₂O₂: sham + infusion of 350 μ M H₂O₂ between d 3 and 7 of life; TPN(-)-L: animals fed exclusively with photoprotected solution of TPN between d 3 and 7 of life; TPN(+)-L: animals fed exclusively between d 3 and 7 of life with light-exposed TPN. Between wk 1 and 14, all animals were fed with regular guinea pig chow. **Panel A**, Plasma triacylglycerol concentrations were lower in groups previously exposed to H₂O₂ or TPN(+)-L. **Panel B**, Hepatic triacylglycerol levels were lower in groups previously exposed to TPN. (Means $\pm$ SEM, $n = 4$ –9, $**p < 0.01$.)

life; plasma TG were also lower in TPN groups ($F_{1,24} = 23.7$) compared with sham groups. In liver (Fig. 1B), TG was lower ($F_{1,24} = 9.5$) only in TPN groups, in which there was no significant light effect ($F_{1,24} = 2.5$). Because the activity of ACC (Fig. 2A), a limiting enzyme in TG synthesis, was similar between groups ($F_{1,25} < 1.1$), a lower availability of substrates, such as acetyl-CoA, to sustain lipid synthesis was suspected. Because acetyl-CoA is an end product of glycolysis, the activities of two key enzymes of this pathway were investigated. Figure 2B and C show that neonatal exposure to i.v. oxidant molecules induced, later in life, greater GK activity ($F_{1,22} = 11.2$) and lower PFK activity ($F_{1,22} = 14.9$). There was no difference related to light exposure of TPN on both enzymes ($F_{1,22} < 0.2$), whereas the difference between TPN and H₂O₂ groups was apparent only for PFK ($F_{1,22} = 9.8$). Thirty-six percent of the variation in plasma TG was explained by PFK activity ($y = 291 \mu\text{M/U} \times x - 959 \mu\text{M}$; $r^2 = 0.36$, $p < 0.01$; Fig. 3), whereas the linear relation between PFK and hepatic TG was not significant ($r^2 = 0.07$). Baseline blood glucose (Fig. 4A) was lower ($F_{1,25} = 11.5$) in animals that received i.v. solutions containing some form of peroxides either as 350 μ M H₂O₂, or as TPN(-)-L that contains ~ 200 μ M peroxides, or TPN(+)-L that is contaminated with ~ 350 μ M peroxides. There was no effect of light ($F_{1,25} = 0.04$) between TPN groups, which were not statistically different from the H₂O₂ group ($F_{1,25} = 4.1$). In contrast, in 30-, 60-, and 90-min postdextrose challenges (Fig. 4B),

Figure 2. Hepatic activity at 14 wk of age of key enzymes for lipogenesis and glycolysis. Sham: control animals fed with regular chow; sham + H_2O_2 : sham + infusion of 350 μM H_2O_2 between d 3 and 7 of life; TPN(-)L: animals fed exclusively with photoprotected solution of TPN between d 3 and 7 of life; TPN(+)L: animals fed exclusively between d 3 and 7 of life with light-exposed TPN. Between wk 1 and 14, all animals were fed with regular chow for guinea pig. ACC activities (A), a limiting step of lipogenesis, did not differ between groups. GK activities (B) were higher in groups previously exposed to i.v. solutions containing peroxides. PFK activities (C) were lower in groups previously exposed to i.v. solutions containing peroxides. (Means $\pm$ SEM, $n = 4-9$, $**p < 0.01$.)

Figure 3. Linear relation between hepatic PFK activity and plasma triacylglycerol concentration at 14 wk of age. The linear relation between PFK-1 activity and triacylglycerol concentration in plasma ($y = 291 \mu\text{M}/\text{U} \times x - 959 \mu\text{M}$; $\text{U} = \text{nmol}/\text{min}/\text{mg}$ protein) was positive ($r^2 = 0.36$) and significant ($p < 0.01$).

blood glucose was significantly higher in the three groups of animals infused earlier with the higher concentrations of oxidant molecules (sham + H_2O_2 and TPN $\pm$ L; $F_{1,94} > 4.3$). After 120 min, blood glucose concentrations were highest in the H_2O_2 group ($F_{1,94} = 3.9$).

Physical phenotype. Adult body weight was affected by the neonatal i.v. feeding regimen (Fig. 5A). At the end of the infusion, by 1 wk of age, body weights did not differ between groups ($F_{1,104} < 0.2$). As early as the first month after the neonatal i.v. feeding challenges, the body weights in the TPN groups were lower ($F_{1,104} = 11.9$) than in the sham $\pm \text{H}_2\text{O}_2$ groups. By 2 and 3 mo of life, all animals fed i.v. during their first wk of life with solutions containing oxidant molecules [sham + H_2O_2 , TPN(+)L, TPN(-)L] had a lower body weight ($F_{1,104} > 12.0$); TPN groups remained the lightest animals ($F_{1,104} > 7.3$). There was no difference between TPN(-)L and TPN(+)L ($F_{1,104} < 2.3$).

Because perturbations in lipid and glucose metabolisms can affect energy production, spontaneous physical activity was monitored as a physiologic marker of energy expenditure (38) and, therefore, availability. Similarly to plasma TG, an additive effect of i.v. oxidant molecules and regimens ($F_{1,26} > 31.2$) was observed on spontaneous physical activity (Fig. 5B). Animals fed i.v. with solutions containing peroxides during their first wk of life were less active later in life.

Figure 4. Blood glucose after fasting or after glucose challenge. Sham (open bar, panel B): control animals fed with regular chow; sham + H_2O_2 (light-gray bar, panel B): sham + infusion of 350 μM H_2O_2 between d 3 and 7 of life; TPN(-)L (dark-gray bar, panel B): animals fed exclusively with photoprotected solution of TPN between d 3 and 7 of life; TPN(+)L (black bar, panel B): animals fed exclusively between d 3 and 7 of life with light-exposed TPN. Between wk 1 and 14, all animals were fed with regular chow for guinea pig. Fasting blood glucose (A), which corresponds to time zero of the glucose challenge, was lower in animals previously exposed to i.v. solutions containing peroxides. Between 30 and 120 min after an i.p. injection of sucrose (B), blood glucose was higher in animals previously exposed to i.v. solutions containing peroxides. Differences between H_2O_2 group and TPN groups were observable at 120 and 150 min after glucose challenge. (Means $\pm$ SEM, $n = 4-9$, $*p < 0.05$; $**p < 0.01$.)

DISCUSSION

The main finding of this study is that neonatal exposure to oxidant molecules such as TPN-generated peroxides will have important consequences, later in life, on lipid and glucose metabolism leading to a phenotype of energy deficiency. Significant developmental changes occur in the metabolic response to a neonatal oxidant challenge between the newborn period when

Figure 5. Body weight and spontaneous ambulatory movement at 14 wk of age. Sham (open bar, panel A): control animals fed with regular chow; sham + H₂O₂ (light-gray bar, panel A): sham + infusion of 350 μ M H₂O₂ between d 3 and 7 of life; TPN(-)L (dark-gray bar, panel A): animals fed exclusively with photoprotected solution of TPN between d 3 and 7 of life; TPN(+)L (black bar, panel A): animals fed exclusively between d 3 and 7 of life with light-exposed TPN. Between wk 1 and 14, all animals were fed with regular chow for guinea pig. The early exposure to TPN induced a lighter body weight (A) from the first month of age onwards, whereas the effect of neonatal exposure to H₂O₂ on body weight was observable by 2 and 3 mo of age. The spontaneous physical activity (B) was decreased in animals exposed previously to peroxides. (Means $\pm$ SEM, $n = 4-9$, ** $p < 0.01$.)

plasma (13) and hepatic (30) TG are increased compared with later in life, a long-time after the time-limited oxidant exposure, when the plasma and liver TG are lower than the control (Fig. 1). This suggests programming of the nutritional metabolic response after early exposure to oxidants.

The long-term effect of early neonatal i.v. exposure to peroxides was separated from the type of nutrition (oral *versus* parenteral; regular chow *versus* TPN). A significant effect induced by the type of nutrition could be explained either by a difference in the quality of nutrients or by the fact that both TPN solutions were contaminated with peroxides. This clinically tested mode of photoprotection (13,14,15) reduces by half the generation of peroxides in TPN solutions (23,25,26). Compared with controls, the similarity of effects on TG and blood glucose observed between the three groups suggests that even the lower amount of neonatal peroxides generated in photoprotected TPN was sufficient to induce modifications in metabolic programming later in life.

The low TG observed at 14 wk of age in animals infused earlier with solutions containing peroxides reveals an abnormal energy metabolism. The absence of modification in ACC activity oriented the investigation toward the availability of the substrate acetyl-CoA to sustain the lipid synthesis. The defect might stem from glucose uptake or the rate of glycolysis. The presence of glucose intolerance (Fig. 4B) suggests resistance to insulin, which

is a powerful modulator of energy metabolism. Unfortunately, in our animal model the concentration of insulin could not be measured to test the possibility of insulin resistance, because no commercial antibody against guinea pig insulin was available. However, the low blood glucose and high GK activity observed in our animals do not support a state of insulin dysregulation. In suckling rats, a high carbohydrate diet was shown to induce, later in life, chronic hyperinsulinemia (39) and poor tolerance to oral glucose challenge (39,40). A chronically high secretion of insulin could explain our observation of low blood glucose and high GK activity. Alternatively, high level of hypoxia inducible factor (HIF)-1 α (41) or hypomethylation of GK gene promoter region (42,43) are potential mechanisms accounting for high GK activity. On the other hand, high activity of GK should favor a greater availability of glucose-derived substrates for acetyl-CoA production from glycolysis. The bottleneck of glycolysis is the PFK activity, which is low in animals infused during their first wk of life with TPN or H₂O₂. The significant correlation ($r^2 = 0.36$) between PFK activity and plasma TG supports the notion that a lower rate of glycolysis could influence plasma lipids. This lower PFK activity could be explained by a greater constitutive degradation of HIF (44) or a lower activity of AMP-activated protein kinase (45). Furthermore, increased fatty acid oxidation in the mitochondrion could generate a large quantity of citrate that would inhibit PFK activity (46). More studies are needed to shed light on these potential mechanisms.

In this study, the impact of early exposure to i.v. oxidant molecules appears to be detrimental to the physical phenotype. The lower body weight and the lower spontaneous activity observed in animals exposed to neonatal i.v. peroxides suggest that these animals produced insufficient energy to support normal growth and physical activity at the same time. In our experimental conditions, a perturbation in glucose metabolism seems to be a key event in the availability of substrates for energy production. In contrast to the initial hypothesis linking the neonatal oxidative load to the metabolic syndrome, our results shows that early exposure to oxidants induces, later in life, a lower level of blood glucose and plasma TG, which are associated to a low spontaneous physical activity when animals exhibit a normal growth rate. Further studies are needed to assess the impact of a neonatal oxidative challenge on body lipid composition in older animals whose energy consumption for growth is decreased.

Globally, the results of this study suggest that modifications in biochemical and physical phenotypes were linked to quality of nutrients early in life. Products of photooxidation would account for differences observed within the TPN groups (TG and physical activity), whereas the similarity of effects linked to TPN and the H₂O₂ load (plasma TG, GK, and PFK activities, blood glucose, body weight, physical activity) suggest that early and short exposure to peroxides has consequences into adulthood. However, the absence from the experimental design of a TPN solution without any peroxides or a sham group with an intermediate H₂O₂ concentration (200 μ M), which would have informed on the peroxide dose effect, represents a limitation of this study that restricts the comparison between TPN and H₂O₂ groups. The more pronounced effects of TPN (-)L on biochemical (TG and PFK) and physical phenotypes (body weight and physical activity) relative to sham + H₂O₂ suggest that compounds other than

H₂O₂ may induce programming of lipid and glucose metabolism. Indeed, other peroxides derived from lipids (47) or ascorbic acid (48) and differences in food intake may also be important confounding variables. Beyond a lack of mechanistic explanation, the study documents an effect of neonatal exposure to H₂O₂ on metabolic programming. Are the observed effects on programming specific to peroxides or generalizable to other sources of oxidants such as oxygen? Neonatal exposure to oxidant molecules is not limited to peroxides from TPN, as many babies receive short periods of oxygen supplementation at delivery. A short period of neonatal oxygen supplementation has been shown to have serious consequences later in life (22,49). Further translational studies will need to investigate the combined effect of both of these clinical relevant sources of oxidants that have been shown to induce different responses in other experimental conditions (50,51).

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