Role of Lipid Peroxidation in Metalloporphyrin-Mediated Phototoxic Reactions in Neonatal Rats

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ABSTRACT. Our group previously demonstrated dose-dependent mortality in neonatal rats treated with tin protoporphyrin and light. We hypothesize that lipid peroxidation may be responsible for the toxic effects of photosensitizing metalloporphyrins. Neonatal rat blood samples with or without metalloporphyrins (40 mM) were exposed to cool white light (20 $\mu\text{W}/\text{cm}^2/\text{nm}$) for 30 min at 37°C. In the *in vivo* model, neonatal rat pups were given injections of 40 μmol of either tin protoporphyrin (4 mM), zinc protoporphyrin/kg body weight, or saline and placed over cool white light. The control animals were similarly treated but kept in the dark. After 3 h, the animals were killed, and their tissues were analyzed for malondialdehyde, conjugated dienes, and disappearance of polyunsaturated fatty acids as indices of lipid peroxidation. In all cases, the known photosensitizer tin protoporphyrin was associated with increased conjugated dienes in the liver and disappearance of polyunsaturated fatty acids and increased malondialdehyde in the liver and brain when animals were exposed to light. Zinc protoporphyrin was not associated with increased lipid peroxidation in the light except in the case of blood *in vitro* where malondialdehyde levels increased. We conclude that lipid peroxidation plays a role in metalloporphyrin-mediated phototoxicity in neonatal rat tissues. (*Pediatr Res* 33: 87-91, 1993)

Abbreviations

MP, metalloporphyrin
SnPP, tin protoporphyrin
ZnPP, zinc protoporphyrin
MDA, malondialdehyde
CD, conjugated diene
PUFA, polyunsaturated fatty acid

MP are being considered in the treatment of neonatal jaundice. These agents are competitive inhibitors of heme oxygenase, the rate-limiting enzyme in bilirubin production. They can therefore prevent the formation and accumulation of bilirubin (1). However, some MP are potential photosensitizers and could react with ambient fluorescent lights or sunlight to lead to tissue damage (1-6). This effect has been demonstrated *in vitro* (6-8) and *in vivo* (2, 9, 10) with SnPP. Our group and others have shown dose-dependent mortality of neonatal rats treated with SnPP and exposed to light (9-11). These same animals did not die when exposed to ZnPP or zinc mesoporphyrin in the presence

of light (9) or when exposed to SnPP in the dark (8, 9). Mimura *et al.* (10) have shown that lipid peroxidation is involved in the phototoxicity of SnPP. Therefore, we attempted to confirm and expand on these findings by examining whether lipid peroxidation plays a role in MP-mediated phototoxicity. To accomplish this, we assessed the tissues of neonatal rats treated with SnPP or ZnPP and exposed to light for evidence of lipid peroxidation.

MATERIALS AND METHODS

Reagents. Metalloporphyrin solutions. Four-mM solutions of SnPP and ZnPP (Porphyrin Products, Inc., Logan, UT) were made by dissolving the MP in 500 μL of 10% (vol/vol) ethanol-amine followed by the addition of 7 mL H_2O . Fifty mg of BSA (Sigma Chemical Co., St. Louis, MO) were added. The pH was titrated to 7.4 with 1.0 N HCl. The volume was then adjusted to 10 mL with distilled water.

Buffer -0.1 M potassium phosphate at pH 7.4 was used in all experiments.

Animals. Suckling Wistar rats (Simonson Laboratories, Gilroy, CA) <48 h of age were used for all experiments. The animals were housed in Stanford's animal facility with their mothers in a temperature-controlled room with a 12-h light cycle before experiments. They were provided with *ad libitum* water and food until the time of exposure.

Experimental Design. Photoirradiation. This was achieved both *in vivo* and *in vitro* using four single strip fixtures (24-inch standard model, Lampi Corporation, Huntsville, AL), which were placed to achieve an irradiance of 20 $\mu\text{W}/\text{cm}^2/\text{nm}$. Cool, white fluorescent tubes (F20T12CW Sylvania, Hillsborough, NH) were used to emit radiation primarily between 450 and 700 nm with a peak at 546 nm. The irradiance achieved is within the range provided by phototherapy in clinical settings.

***In vitro* experiments.** Twenty μL of blood drawn from animals <48 h old were mixed with 20 μL of KPO_4 in 2-mL septum-sealed clear glass vials (Alltech Associates, Inc., Deerfield, IL). One half μL of either ZnPP or SnPP (4 mM) was added to the vials. Light-deprived controls were similarly prepared in amber vials and shielded from the light. The vials were temperature-equilibrated for 5 min in a 37°C bath with a 10-mm-thick Plexiglass bottom. Light-driven reactions were carried out in the water bath. The temperature was maintained at 37°C $\pm$ 0.5°C with a water-circulating heater. The reaction was conducted for 30 min at 37°C and terminated by quick-freezing the vials in pulverized dry ice (-78°C).

***In vivo* experiments.** Animals were randomly assigned to treatment groups of two animals each and were administered intraperitoneal injections of 40 μmol of SnPP or ZnPP/kg body weight, respectively. Controls were given injections of equal volumes of normal saline. Upon completion of a 1-h equilibration period, the pairs were weighed and then placed in sealed glass chambers supplied with water-free air. The chambers were placed on a Plexiglas shield over the light source. The air temperature around

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the apparatus was kept at approximately 27°C by cooling fans. The chambers were supplied with water-free air at a flow rate of 40 mL/min. After a 3-h exposure, animals were weighed. Light-deprived controls were similarly treated except that chambers were shielded from the light.

Methods. All tissue preparation and all assays were conducted in reduced lighting to obviate the effect of light on MP in the preparations.

Tissue preparation. The animals were anesthetized with carbon dioxide, and blood was drawn through an intracardiac puncture. The animals were then killed by decapitation, and tissues (liver, lung, brain, heart, and spleen) were removed and homogenized with buffer in preparation for analysis.

Assessment of lipid peroxidation. MDA production, an index of lipid peroxidation, was measured via the method of Asakawa and Matsushita (12).

CD were measured by minor modifications of the methods of Recknagel and Glende (13). Samples were extracted twice with 2:1 chloroform methanol heated to 45°C. The chloroform layers were pooled, acidified water (pH 2.5) was added, and the lower layer was extracted and dried in a Speed-Vac vacuum extractor (Savant Instruments, Inc., Farmingdale, NY) and then resuspended in cyclohexane and read at an absorbance of 233 nm.

Changes in PUFA content of fatty tissues were assessed as follows. Homogenates were extracted with 2:1 chloroform methanol at a ratio of 4:1 with the sample volume. Fatty-acid methyl esters were prepared by the methods of Roberts and Rosenberry (14) and analyzed on a Shimadzu GC14 (Shimadzu Scientific Instruments, Inc., Columbia, MD) gas chromatograph equipped with a 30-m, 0.25-mm inner diameter Supelco column (Supelco Inc., Bellefonte, PA) at a 1:100 split ratio, a flame ionization detector, and a Shimadzu C-R4A chromatopac integrator. The carrier gas was helium at 15 pounds per square inch, and the column temperature was programmed from 150 to 280°C at 6°C/min $\times$ 18 min and then 8°C/min $\times$ 12 min. Retention times of sample peaks were compared with those of authentic fatty-acid methyl esters of 14 to 22 chain lengths (PUFA 2 Supelco). Pentadecanoic acid (C15:0) was added in the samples as an internal standard. Fatty-acid weights were calculated from comparison of the integrated area of the identified peak to that of C15:0.

Measurement of protein. Protein content was measured using the methods of Lowry *et al.* (15).

Statistical analysis. Lipid peroxidation values were expressed as μmol of MDA/mg protein. Each value was compared with its control (*i.e.* light control for light-exposed animals given injections of ZnPP or SnPP and dark control for animals given injections of ZnPP and SnPP and maintained in the dark). Values were ultimately expressed as percentage change in control:

$$\frac{\text{Sample} - \text{control}}{\text{Control}} \times 100$$

PUFA content was expressed as the percentage of PUFA in each sample.

For comparison between treatment groups, the null hypothesis that there was no difference between treatment means for a given value was tested by single-factor analysis of variance. Statistical significance ($p < 0.05$) between and within groups was determined by means of the Scheffe, Fisher, and Dunnett methods of multiple comparisons.

RESULTS

In Vitro Studies. MDA was significantly increased in both SnPP- and ZnPP-treated samples exposed to light compared with controls. No increase in MDA was noted when samples were kept in the dark (Fig. 1).

In Vivo Studies. No animals died during the exposure periods, but in six of 10 experiments the SnPP-treated animals exposed to light appeared morbid at the end of the exposure period.

Fig. 1. Change in MDA content of neonatal rat blood after exposure to MP and light *in vivo*. Values are expressed as the percentage of control $\pm$ standard error; $n = 9$ in all groups. *, Significantly different from light and light-deprived controls ($p < 0.05$); †, significantly different from ZnPP-treated animals exposed to light.

Lipid Peroxidation: MDA. The homogenates of liver, brain, and blood obtained from animals exposed to light and given injections of SnPP had significantly increased MDA content over control and over ZnPP-treated animals. None of the tissues from ZnPP-treated animals had significant increases in MDA content over controls. All light-deprived animals, whether given injections of ZnPP or SnPP, showed no change in MDA content of tissues over control (Fig. 2). No changes in MDA content were observed in other tissues assessed (lung, heart, or spleen). Therefore, CD and fatty-acid profiles were not assessed in these tissues.

CD. Content of CD increased in liver tissue of animals treated with SnPP and exposed to light compared with all other conditions. No significant differences were seen in CD content of brain tissue (Fig. 3).

PUFA content decreased significantly in liver and brain tissues of rats treated with SnPP and light exposure compared with all light-exposed and -deprived controls (Fig. 4).

Weight loss. All animals exhibited weight loss when maintained in the exposure chambers. However, SnPP-treated animals exposed to light had a significant loss of weight compared with ZnPP-treated animals and controls (Fig. 5).

DISCUSSION

We have shown that neonatal rats exposed to SnPP and light demonstrate increased lipid peroxidation *in vitro* in the blood as well as increased lipid peroxidation in the liver, brain, and blood *in vivo*. Although this does not demonstrate a cause-and-effect relationship between phototoxicity-mediated mortality and lipid peroxidation, it suggests an association between the two. Previous *in vitro* studies demonstrated that SnPP can be activated by photons, leading to an excited state of the porphyrin structure (3, 4, 16). This molecule can then be quenched by molecular oxygen yielding singlet oxygen, a toxic molecule known to cause cell damage, and a relaxed porphyrin. Keino *et al.* (11) showed increased MDA formation in rat erythrocytes incubated with similar concentrations of SnPP compared with controls. An *in vivo* study by this group showed increased lipid peroxidation in whole rat-blood after SnPP and light exposure (10). They did not, however, look at the *in vivo* effect of photoirradiation on rat tissues as we did. We believe this is the first report of *in vivo* lipid peroxidation in brain and liver tissues due to photosensitization of SnPP.

Brain tissues increased MDA content and decreased PUFA when animals were treated with SnPP and exposed to light, but no significant changes were observed in CD content compared with controls. CD are formed at the initiation of lipid peroxidation reactions. These compounds can react dynamically with

Conditions

Fig. 2. Change in MDA content of various neonatal rat tissues after exposure to MP and light *in vivo*. A, blood; B, brain; C, liver. Values are expressed as the percentage of control $\pm$ standard error. $n = 10$ in all groups. *, Significantly different from light and light-deprived controls ($p < 0.05$); †, significantly different from ZnPP-treated animals exposed to light.

other substrates or be decomposed in the presence of metal ions (17). MDA, by contrast, is a byproduct of lipid peroxidation that mostly forms during the heating step of the thiobarbituric acid reaction and reflects a more static, albeit less specific index of lipid peroxidation (17, 18). Because we also have evidence of PUFA loss in brain tissue of animals treated with SnPP and exposed to light, we speculate that lipid peroxidation did occur in this case, but that the diene products reacted with other compounds, propagating injury, demonstrated as MDA and loss of PUFA.

ZnPP has previously been investigated in our laboratory using neonatal rhesus monkeys (19, 20). These animals received doses of ZnPP and had effective lowering of heme oxygenase activity as demonstrated by carbon monoxide excretion rate reduction and decreased heme oxygenase activity in the liver and spleen. Hintz *et al.* (9) showed no adverse effect of ZnPP in neonatal rats treated with this compound and exposed to light for 12 h. The observation that lipid peroxidation occurred *in vitro* with ZnPP in neonatal rat blood is consistent with previous studies reported by us demonstrating a mild phototoxic effect of ZnPP, by a different technique, in a similar preparation *in vitro* (6, 8). In contradistinction, light exposure did not result in lipid peroxidation in the brain, liver, or blood of neonatal rats exposed to light and ZnPP *in vivo*. Preliminary studies done in our laboratory demonstrated that ZnPP was not found in neonatal rat brain samples after the 3-h exposure period (unpublished observations), and it has previously been shown that ZnPP does not cross the blood-brain barrier, unlike SnPP (21). It is well

Conditions

Fig. 3. Change in CD content of neonatal rat tissues after exposure to MP and light *in vivo*. A, liver; B, brain. Values are expressed as the percentage of change in control $\pm$ standard error. $n = 6$ in all groups. *, Significantly different from light and light-deprived controls ($p < 0.05$); †, significantly different from ZnPP-treated animals exposed to light.

Fig. 4. Percentage of PUFA content of neonatal rat tissues after exposure to MP and light *in vivo*. A, liver; B, brain; $n = 4$ in all groups. *, Significantly different for light and light-deprived controls ($p < 0.05$); †, significantly different from ZnPP-treated animals exposed to light.

Fig. 5. Change in body weight in neonatal rats exposed to MP and light values are expressed as the percentage of control $\pm$ standard error. $n = 7$ in all groups. *, Significantly different from light and light-deprived controls ($p < 0.05$); †, significantly different from ZnPP-treated animals exposed to light.

known, however, that ZnPP enters the liver (20–22), yet it did not have any toxic effects there. It was suggested by Greenbaum and Kappas (5) that perhaps all of the ZnPP administered *in vivo* could be rapidly inactivated by photodegradation and thus no longer be available to tissues. Studies conducted in our laboratory indicate otherwise. In fact, ZnPP was detected in neonatal rat tissues for several days after an intraperitoneal injection (23). It could be that ZnPP does not reach tissues as efficiently as SnPP, but studies conducted for longer periods of time than ours (*i.e.* 12 h) showed no phototoxic effect of ZnPP (9–11). Furthermore, we conducted preliminary studies in neonatal rats given injections of ZnPP on the 1st d of life and exposed the 3rd d of life, when maximal HO inhibitory effect is noted after intraperitoneal injection (Rodgers PA, personal communication), and saw no phototoxicity of ZnPP *in vivo* (unpublished observations). Collectively, these data suggest that ZnPP is in a circumstance *in vivo* in which it is unable to interact with light while remaining enzymatically efficient.

We saw an SnPP-stimulated loss in total body weight, probably reflecting water loss in rat pups exposed to light. Hintz *et al.* (9) saw a similar effect. It is unclear how this effect is mediated, although it may be due to lipid peroxidative damage in tissues leading to altered cell and membrane function (24–27). The animals were more agitated and sweated during treatment with SnPP and exposure to light, suggesting skin and respiratory water losses and/or increased metabolism.

Our study has shown evidence of lipid peroxidation in liver, blood, and brain tissue of neonatal rats exposed to SnPP and light but not when exposed to ZnPP and light. MP competitively inhibit HO, the rate-limiting enzyme in bilirubin production. This may lead to decreased levels of bilirubin, a known quencher of singlet oxygen (28). This is unlikely to result in an immediate decrease in bilirubin levels in our model because animals are given injections and exposed in rapid succession. Alternately, SnPP can photodegrade bilirubin *in vitro*, which then would then result in an immediate lowering of bilirubin (29). Nonetheless, Wistar rats have low levels of bilirubin, and whether a decrease in an already low bilirubin level would cause a significant increase in lipid peroxidation is unclear, but unlikely.

The relevance of this study to the human neonate is unknown. However, it is of interest that human neonates do have decreased antioxidant defenses in the first few days of life when β -carotene (30), glutathione, vitamin E, and catalase are at very low levels (31); these substances gradually increase over the first few days of life (32). Singlet oxygen is primarily quenched by carotenes (30). Therefore, a deficiency of β -carotene in early neonatal life could lead to increased vulnerability to lipid peroxidative damage caused by compounds such as SnPP. Neonatal red blood cells are particularly susceptible to oxidative damage (33). Neonatal tissues may also be particularly vulnerable to lipid peroxidation, as is known to be the case in animals such as neonatal rats, who are generally more susceptible to lipid peroxidation of liver

tissues than adults (34). Premature rats are potentially at a greater disadvantage because their antioxidant defenses are even more immature (35), and use of photosensitizing MP could have adverse consequences, such as aggravation of retinopathy of prematurity, bronchopulmonary dysplasia, and necrotizing enterocolitis. These conditions have been linked to oxygen radical injury in the premature infant (36–38). Further studies are needed to determine whether MP are safe and should be considered for potential clinical use.

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Announcement

The National Council of Jewish Women Center for the Child, in collaboration with the Society for Research in Child Development, has been awarded the contract by The Administration on Children, Youth and Families to hold the second national Head Start research conference, entitled "Translating Research into Practice: Implications for Serving Families with Young Children," on November 4-7, 1993 in Washington, DC. Following the success of the first Head Start research conference, "New Directions in Child and Family Research: Shaping Head Start in the Nineties," the major goals of the second conference are to identify and disseminate current research in early childhood and families, discuss child and family issues, and identify new research and program needs. A special focus will be on translating research into practice in an effort to help practitioners serving low-income families gain a better understanding of effective early childhood interventions and programming. *For additional information, contact* Faith Lamb Parker, Ph.D., Project Director, Head Start Research Projects, NCJW Center for the Child, 53 West 23rd Street, New York, NY 10010, (212) 645-4048.

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