Prostaglandin E₂ Attenuates Hyperoxia-Induced Injury in Cultured Rabbit Tracheal Epithelial Cells

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ABSTRACT. We assessed the kinetics of hyperoxia-induced prostaglandin E₂ (PGE₂) production by cultured rabbit tracheal epithelial (TE) cells with different inherent capacities to generate PGE₂ and the role of endogenous PGE₂ production in protecting these cells from hyperoxic injury. Rabbit TE cells grown to confluence with or without lipid supplements [0.1% Excyte III (Miles-Pentex) and 1 μ M arachidonic acid] were exposed for 2 h to control (5% CO₂/air) or hyperoxic (5% CO₂/90% O₂) atmospheres at a gas-fluid interface. Serial cell culture effluents collected during exposure were analyzed for PGE₂ by enzyme-linked immunoassay. Basal PGE₂ production by lipid-supplemented cells was approximately 3-fold greater than that by unsupplemented cultures ($p < 0.01$). In lipid-supplemented cells, PGE₂ production doubled after 15 min of hyperoxic exposure ($p < 0.05$) and then declined to approximately 50% of initial levels, whereas exposure to 5% CO₂/air did not significantly change PGE₂ production. In unsupplemented cells, neither control nor hyperoxic exposure altered PGE₂ production. Hyperoxia-exposed TE cells had decreased ability to convert 10 μ M exogenous arachidonic acid to PGE₂, suggesting hyperoxia-induced inhibition of the enzymes involved in PGE₂ synthesis. Lipid-supplemented cells were less susceptible to hyperoxic injury than unsupplemented monolayers, as evidenced by increased viability (trypan blue exclusion) and decreased generation of lipid peroxides (thiobarbituric acid reactive substances). Addition of exogenous PGE₂ to unsupplemented cultures at concentrations that were produced by lipid-supplemented cells (2 ng/mL every 15 min) during hyperoxic exposure eliminated these differences in hyperoxia-induced lipid peroxidation and cytotoxicity. Our observations suggest that hyperoxic exposure inhibits TE cell cyclooxygenase activity and that endogenously produced airway epithelial cell PGE₂ has a cytoprotective role against hyperoxia-induced injury. (*Pediatr Res* 32: 87-91, 1992)

Abbreviations

TE, tracheal epithelial
PGE₂, prostaglandin E₂

HBSS, Hanks' balanced salt solution
T₀, initial 15-min equilibration period

We have reported that rabbit and human TE cells cultured in serum-free media supplemented with a commercial phospholipid extract and exogenous arachidonic acid have fatty acid profiles more similar to those of respective native airway epithelium compared to TE cells grown without lipid supplements (1, 2) and that lipid-supplemented TE monolayers are more resistant to hyperoxic injury than unsupplemented cells (2, 3). We have also observed that lipid-supplemented TE cells have a higher basal production of PGE₂ than companion unsupplemented cultures, and in lipid-supplemented human TE cells, increased PGE₂ production apparently results from increased total cellular content and availability of arachidonic acid rather than from changes in cyclooxygenase activity (4). Because PGE₂ is known to have cytoprotective and antiinflammatory properties (5-7) and E series prostaglandins can decrease pulmonary injury induced by various insults (8, 9), we speculated that the increased capacity to generate PGE₂ in lipid-supplemented TE cells might have a role in protecting these cells from hyperoxic injury.

In the present report, we investigated the kinetics of PGE₂ production by rabbit TE monolayers grown in serum-free media with or without lipid supplementation during 2-h exposures to hyperoxic or normoxic atmospheres and assessed whether PGE₂ attenuates hyperoxia-induced cellular injury. We found that although hyperoxic exposure initially stimulated PGE₂ production, at later times PGE₂ production by hyperoxia-exposed TE cells was reduced, apparently as a result of inhibition of the enzymes involved in PGE₂ synthesis. We also observed that exogenous PGE₂ provided to the TE monolayers during the course of hyperoxic exposure decreased hyperoxia-induced lipid peroxidation and cytotoxicity.

MATERIALS AND METHODS

Lipid supplementation of cultured TE cells. Tracheal epithelial cells recovered from New Zealand White rabbits by enzyme dissociation were plated onto collagen-coated modified 35-mm glass Petri dishes in serum-free Hams F-12 media containing hormones and growth factors as previously described (2, 10). After 48 h, the serum-free growth media of half of the cultures established from a given trachea were further supplemented with 0.1% Excyte III (Miles-Pentex, Kankakee, IL), a phospholipid-rich lipoprotein extract, and 1 μ M arachidonic acid complexed to fatty acid-free BSA at a molar ratio of 3.3:1 (11). This combination of exogenous lipids ("lipid supplementation") added to serum-free media results in fatty acid profiles and

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arachidonic acid content in cultured rabbit TE cells that more closely resemble those of freshly isolated TE cells, whereas cells maintained in serum-free media without lipid supplements develop abnormal fatty acid profiles characteristic of essential fatty acid deficiency, including a marked depletion of total cellular arachidonic acid (1, 2). Growth medium was changed every 48 h, and confluent monolayers were achieved in 7–10 d.

Exposure of TE monolayers to hyperoxia. The TE monolayers were exposed to hyperoxic (~90% O₂ in 5% CO₂) or control (5% CO₂/air) atmospheres for 2 h at a gas-fluid interface using a system that allows for serial recovery of cell culture effluents during the course of exposure (described in detail in Refs. 2 and 12). Briefly, confluent TE monolayers were rinsed and covered with 2 mL of HBSS (Gibco, Grand Island, NY) containing Ca⁺⁺ and Mg⁺⁺, and the culture dishes were positioned on a rocker platform inside a stainless steel "Rochester chamber" enclosed in a 37°C incubator. Humidified control or hyperoxic atmospheres were introduced into the chamber, and after 15 min of equilibration the platform was tilted, draining the media off each culture and leaving only a film of fluid adhering to the cells. The thin layer of fluid overlying the cells was renewed by flooding each culture dish with HBSS (2 mL, 20-s delivery) every 15 min and then immediately tilting the platform. Three or four monolayer cultures established from the same rabbit trachea were exposed concurrently either to control or to hyperoxic atmospheres. The HBSS media covering the cultures during the initial 15-min equilibration period (T₀) and subsequent HBSS effluents during the course of exposure were collected individually from each culture into silanized glass bottles maintained on ice. HBSS was used during the exposure protocols to obviate oxidation of growth media components. We have previously observed that rabbit TE cultures can be maintained in this system exposed to a humidified 5% CO₂/air atmosphere for more than 2 h without physical disruption of the monolayers or significant loss of cell viability (2).

Quantitation of PGE₂ in TE cell effluents. The release of PGE₂ by TE monolayers into HBSS effluents was assessed by enzyme immunoassay, as described by Pradelles *et al.* (13), using commercial antisera and tracer obtained from Cayman Chemicals (Ann Arbor, MI). The assay was performed on unfractionated media based on experiments in which 16 media samples were assayed by enzyme immunoassay directly or after C18 SepPak cartridge (Waters, Milford, MA) extraction; correlation of the two values was 0.99 by linear regression analysis, with the value after SepPak extraction equal to 82% of the direct assay value. The lower limit of detection of the assay is 3.8 pg/mL. In addition to the cross-reactivities reported by the manufacturer, we have determined that this antisera has less than 0.3% cross-reactivity with arachidonic acid or with 12- or 15-hydroxyeicosatetraenoic acid. Recovery of authentic PGE₂ (20–50 ng) applied to collagen-coated culture dishes inside the chamber and exposed for 15 min to 5% CO₂/air was approximately 90%. After 15 min of exposure to hyperoxic atmospheres, recovery of PGE₂ was not appreciably decreased.

Measurement of cell viability and lipid peroxide content. After control or hyperoxic exposures, the TE cells were recovered from the culture dishes by brief digestion with 0.5% trypsin/EDTA (Gibco). Cell viability (trypan blue dye exclusion) and number were determined by hemocytometer, and the lipid peroxide content of TE cells was assessed by measurement of thiobarbituric acid-reactive substances. A modification of the method of Ohkawa *et al.* (14) was employed as in previous studies (2, 12), using fluorescent spectrophotometry to enhance assay sensitivity and permit detection of subnanomolar quantities of thiobarbituric acid-reactive substances. Lipid peroxide content was expressed as nmol of malondialdehyde per 10⁶ cells; values for duplicate measurements of the same sample varied by less than 10%.

Addition of exogenous PGE₂ during control or hyperoxic exposure. To assess whether PGE₂ might have a role in protecting

rabbit TE cells from hyperoxic injury, in some experiments exogenous PGE₂ was provided to the cultures during the course of control or hyperoxic exposure. This was accomplished by adding 1 ng/mL PGE₂ (Sigma Chemical Co., St. Louis, MO) to the reservoir of HBSS media used to periodically renew the film of fluid overlying the cultures during gaseous exposure (2 ng of PGE₂ provided every 15 min). This concentration of exogenous PGE₂ was selected to approximate PGE₂ concentrations achieved by lipid-supplemented monolayers under basal conditions. After exposure, the cells were recovered for determination of cell number, viability, and lipid peroxide content.

Assessment of cyclooxygenase activity after control or hyperoxic exposure. To investigate whether changes in PGE₂ production observed during hyperoxic exposure might be due to decreased activity of enzymes involved in PGE₂ synthesis, the ability of TE monolayers to convert exogenous arachidonic acid to PGE₂ was assessed by incubating each culture with 10 μM arachidonic acid (Cayman Chemicals) in HBSS at 37°C for 15 min immediately after the 2-h control or hyperoxic exposures. The media were then collected and analyzed for PGE₂. This concentration of arachidonic acid and incubation time were found to be optimal for PGE₂ production (unpublished observations).

Statistical analysis. Changes in cell viability, lipid peroxide content, and conversion of exogenous arachidonic acid to PGE₂ after control or hyperoxic exposures were assessed by analysis of variance and the Student-Newman-Keuls test. The unpaired *t* test was used to compare differences in PGE₂ production between lipid-supplemented and unsupplemented TE monolayers at a given time of exposure, and the kinetics of PGE₂ production by individual cultures during the course of exposures was assessed by multivariate analysis of variance subjected to *post hoc* Scheffe procedure. Significance was considered at a *p* value of less than 0.05.

RESULTS

Release of PGE₂ into effluent media. The kinetics of PGE₂ production by rabbit TE monolayers during the course of exposure to control or hyperoxic atmospheres is shown in Figure 1.

Fig. 1. Kinetics of PGE₂ production by rabbit TE monolayers exposed to hyperoxia or 5% CO₂/air. Serial HBSS cell culture effluents were collected from individual monolayer cultures during the course of 2-h exposures to either 5% CO₂/air or hyperoxia and analyzed by enzyme immunoassay for PGE₂. Data are means ± SEM, *n* = 12–14 cultures in each condition. *, *p* < 0.05, lipid-supplemented, hyperoxia vs unsupplemented, hyperoxia. **, *p* < 0.01, lipid-supplemented, hyperoxia vs unsupplemented, hyperoxia. †, *p* < 0.05, lipid-supplemented, 5% CO₂/air vs lipid-supplemented, hyperoxia.

As in our previous studies (4), basal (T_0) production of PGE₂ by lipid-supplemented TE monolayers was approximately 3-fold greater than that by lipid-unsupplemented cells ($p < 0.01$). In lipid-supplemented cultures, production of PGE₂ doubled after 15 min of hyperoxic exposure and then declined to approximately 50% of initial levels. However, during continued hyperoxic exposure, PGE₂ production by lipid-supplemented cells still exceeded that of unsupplemented monolayers by about 2-fold ($p < 0.05$ at 2 h). Exposure of lipid-supplemented TE monolayers to control normoxic atmospheres also caused an initial increase in PGE₂ production after 15 min of exposure, although this increase was not statistically significant. With continued exposure to 5% CO₂/air, PGE₂ production by lipid-supplemented cells returned to levels comparable to basal T_0 values. Lipid-unsupplemented TE cultures exhibited no significant changes in PGE₂ production throughout the 2-h exposures to either hyperoxic or control atmospheres.

Metabolism of exogenous arachidonic acid to PGE₂ by TE monolayers after exposure to control or hyperoxic atmospheres. To determine if the reduced production of PGE₂ after hyperoxic exposure resulted from inhibition of the enzymes responsible for PGE synthesis, metabolism of excess free exogenous arachidonic acid to PGE₂ was assessed as a measure of maximal prostaglandin synthesis (Fig. 2). After exposure to hyperoxic atmospheres, the ability of lipid-supplemented and -unsupplemented TE cells to convert exogenous arachidonic acid to PGE₂ was reduced by approximately 50% compared to normoxia-exposed cultures. This reduction was not the result of decreased cell number or viability after hyperoxic exposure. There was no significant loss of cells from the culture dishes after either exposure (data not shown). Although viability was reduced after hyperoxic exposure (normoxic *versus* hyperoxic exposure, lipid-unsupplemented $86.4 \pm 2.2\%$ *versus* $71.1 \pm 2.8\%$; lipid-supplemented $90.7 \pm 1.4\%$ *versus* $83.3 \pm 2.9\%$), these decreases in viability were not of sufficient magnitude to account for the observed decreases in PGE₂ production. In lipid-supplemented and -unsupplemented cells exposed to 5% CO₂/air, addition of exogenous arachidonic acid resulted in comparable increased PGE₂ production to levels that were 10- to 20-fold greater than basal T_0 values.

Effect of exogenous PGE₂ on TE cell viability and lipid peroxide content after control or hyperoxic exposure. Exposure to

control 5% CO₂/air atmospheres did not significantly affect the viability of either lipid-unsupplemented or -supplemented cultures (viability of unexposed monolayers was 92–94%) (Table 1). Although hyperoxic exposure resulted in decreased viability in both lipid-supplemented and -unsupplemented cultures, hyperoxia-induced cytotoxicity was significantly greater in lipid-unsupplemented monolayers. The addition of exogenous PGE₂ at 1 ng/mL to unsupplemented cultures during hyperoxic exposure significantly increased TE cell viability ($79.3 \pm 4.4\%$ *versus* $70.3 \pm 1.8\%$, $p < 0.05$) to the levels seen in hyperoxia-exposed lipid-supplemented cells ($80.6 \pm 1.9\%$). The addition of PGE₂ to lipid-supplemented cultures during hyperoxic exposure resulted in a further (although not statistically significant) increase in viability (to $87.1 \pm 1.1\%$). In both lipid-supplemented and -unsupplemented cultures, addition of PGE₂ during the course of exposure to 5% CO₂/air had no effect on cell viability. Increased lipid peroxides were detected concomitant with decreased viability in both lipid-supplemented and -unsupplemented TE cultures exposed to hyperoxia (Table 1). Providing exogenous PGE₂ to unsupplemented cultures during hyperoxic exposure reduced lipid peroxide formation (0.21 ± 0.07 *versus* 0.48 ± 0.14 nmol malondialdehyde, $p < 0.05$).

Interestingly, addition of exogenous PGE₂ to the cultures during exposure to hyperoxic atmospheres did not protect against hyperoxia-induced inhibition of PGE₂ synthesis. When exposed to hyperoxia in the presence of 1 ng/mL PGE₂ and then incubated with 10 μ M arachidonic acid, total PGE₂ production (ng/10⁶ cells, mean $\pm$ SEM, $n = 4$) was 5.2 ± 0.5 and 4.7 ± 1.1 in unsupplemented and lipid-supplemented cultures, respectively, values that are not statistically different from those of respective hyperoxia-exposed cultures not provided with exogenous PGE₂ (Fig. 2).

DISCUSSION

In this report, we examined the effect of hyperoxia on PGE₂ production by rabbit TE cells with different inherent capacities to generate PGE₂ and assessed whether increased PGE₂ production might have a role in protecting these cells from hyperoxic injury. We postulated that if increased PGE₂ production protects lipid-supplemented cells against hyperoxia-induced injury, then providing lipid-unsupplemented TE cells with comparable amounts of PGE₂ during hyperoxic exposure should also protect these cells from hyperoxic injury.

Lipid-supplemented TE monolayers exhibited a biphasic response of PGE₂ production during the course of a 2-h exposure to hyperoxia. A 2-fold increase in PGE₂ production over preexposure levels was observed after 15 min of hyperoxic exposure, followed by a decline in PGE₂ production to levels that remained significantly greater than those of control or hyperoxia-exposed unsupplemented cells. Unsupplemented TE monolayers did not demonstrate a similar initial increase in PGE₂ synthesis when exposed to hyperoxic atmospheres, presumably because PGE₂ production in these cells is limited by the availability of endogenous arachidonic acid. Because maximal PGE₂ production in response to incubation with excess free exogenous arachidonic acid was the same in normoxia-exposed lipid-supplemented and -unsupplemented cultures (Fig. 2), the activity of cyclooxygenase enzymes is similar in these cells. Thus, the decreased PGE₂ production observed in lipid-unsupplemented cells apparently results from decreased cellular content of arachidonic acid, rather than from reduced metabolic enzyme activity. This observation and the inference that the enzymes responsible for PGE₂ synthesis in rabbit TE cells are not altered by lipid supplementation are consistent with our previous studies with human TE cells (4).

In the lipid-supplemented TE cells, decreased production of PGE₂ after the initial increase in response to hyperoxic exposure could conceivably be due to either autocatalyzed inactivation and/or to hyperoxia-induced inhibition of cyclooxygenase enzyme activities. Our studies do not allow us to assess the relative

Fig. 2. Effect of hyperoxic or 5% CO₂/air exposure on the metabolism of exogenous arachidonic acid to PGE₂. Immediately after 2-h exposures to either 5% CO₂/air or hyperoxic atmospheres, the cultures were incubated with 10 μ M arachidonic acid in HBSS for 15 min at 37°C and PGE₂ content of HBSS media was assessed by enzyme immunoassay. Data are means $\pm$ SEM, $n = 4$ individual cultures per condition. *, $p < 0.05$ vs 5% CO₂/air, similar culture conditions.

Table 1. Viability and lipid peroxide content of lipid supplemented and unsupplemented rabbit TE cells exposed to 5% CO₂/air or hyperoxic atmospheres: effect of exogenous PGE₂*

	Exogenous PGE ₂ during exposure	TE cell culture conditions			
		Lipid unsupplemented		Lipid supplemented	
		5% CO ₂ /air	Hyperoxia	5% CO ₂ /air	Hyperoxia
Cell viability (%)	None	88.5 ± 1.5	70.3 ± 1.8†	90.9 ± 1.6	80.6 ± 1.9†‡
	1 ng/mL	87.4 ± 2.8	79.3 ± 4.4†§	88.5 ± 2.5	87.1 ± 1.1
Lipid peroxides	None	0.08 ± 0.03	0.48 ± 0.14†	0.04 ± 0.01	0.27 ± 0.06†
(nmol MDA/ 10 ⁶ cells)‖	1 ng/mL	0.11 ± 0.03	0.21 ± 0.07†§	0.08 ± 0.03	0.15 ± 0.03§

* Data are means ± SEM from cultures established from seven individual rabbit trachea. In each experiment, three or four 35-mm culture dishes were pooled for analysis as a single sample.

† $p < 0.05$ vs 5% CO₂/air exposed controls grown in similar culture conditions.

‡ $p < 0.05$ vs similarly exposed lipid unsupplemented TE cells.

§ $p < 0.05$ vs similarly exposed TE cultures not provided with exogenous PGE₂ during exposures.

‖ MDA, malondialdehyde.

contribution of either mechanism to the observed decrease in enzyme activity. However, two observations suggest that hyperoxia-induced inhibition is the predominant mechanism; there was no initial burst of PGE₂ synthesis in hyperoxia-exposed lipid-unsupplemented cells and thus no autocatalyzed inactivation, but, nonetheless, the metabolism of exogenous arachidonic acid to PGE₂ was equally inhibited by hyperoxia in both lipid-supplemented and -unsupplemented cells (Fig. 2). These observations also suggest that hyperoxia-induced inhibition of the enzyme(s) involved in PGE₂ synthesis is not affected by cellular fatty acid composition.

Inhibition of cyclooxygenase enzyme activities and decreased cyclooxygenase metabolite production have been reported by other investigators after *in vitro* exposure of cultured cells to hyperoxic atmospheres or to ozone (15–17). Sporn *et al.* (16) exposed pulmonary macrophages to hyperoxic atmospheres and observed an apparent inhibition of PGE₂ isomerase but no evidence of decreased thromboxane synthetase activity. Madden *et al.* (17) noted selective inhibition of cyclooxygenase, but not prostacyclin synthetase, in cultured bovine pulmonary endothelial cells exposed to ozone. In our studies, it remains to be determined whether cyclooxygenase and/or PGE₂ isomerase are directly inactivated by hyperoxic exposure or, alternatively, whether additional products generated during hyperoxic exposure might inhibit the activity of these enzymes. Oxidative degradation of PGE₂ is an unlikely explanation for the decreased PGE₂ production detected during hyperoxic exposure, inasmuch as other investigators have reported no degradation of PGE₂ even after direct incubation with high concentrations of hydrogen peroxide (18).

The biphasic response of PGE₂ production observed in hyperoxia-exposed, lipid-supplemented TE cells indicates an initial activation of cyclooxygenase metabolism before subsequent inhibition. In other studies assessing the kinetics of cyclooxygenase metabolite production in response to oxidant stress, evidence of initial activation of cyclooxygenase metabolism was not detected. For example, no initial increase in prostacyclin synthesis was observed by Madden *et al.* (17) in endothelial cells after 5 min of exposure to 1 ppm ozone. However, if the endothelial cells were exposed to ozone in the presence of catalase, a 28% increase in prostacyclin production was seen at 5 min, and after 30 min of ozone exposure prostacyclin production was further increased by more than 150% compared to air-exposed cultures. These same investigators also demonstrated that endothelial cell prostacyclin synthesis decreased with direct incubation of the cultures with 75 or 100 μ M hydrogen peroxide, but not after incubation with 50 μ M. Collectively, these observations suggest that the intensity of the initial oxidant stress may be an important determinant as to whether cyclooxygenase metabolic activity is enhanced before subsequent oxidant-induced inhibition.

The increased capacity of lipid-supplemented TE cells to pro-

duce PGE₂, both under basal conditions and throughout the course of hyperoxic exposure, appears to play a role in the decreased susceptibility of these cells to hyperoxia-induced lipid peroxidation and cytotoxicity. The addition of exogenous PGE₂ to unsupplemented TE cultures during hyperoxic exposure, at concentrations produced by lipid-supplemented cultures, eliminated the differences in hyperoxia-induced mortality between cells in the two culture conditions, and also reduced lipid peroxide generation in unsupplemented TE cultures. In a recent report (19), exogenous PGE₂ at concentrations ranging from 1 to 10 μ g/mL was shown to protect cultured bovine bronchial cells from endotoxin-induced injury. In our studies with rabbit TE cells, a protective effect of PGE₂ against hyperoxia-induced injury was observed using considerably lower concentrations of PGE₂ (1 ng/mL, 2 ng provided every 15 min). Because we did not analyze HBSS effluent media for eicosanoids other than PGE₂, we cannot exclude the potential contributions of other metabolites of arachidonic acid generated by rabbit TE cells to the observed differences in susceptibility to hyperoxic injury.

Our previous study demonstrating that lipid-supplemented rabbit TE cells were more tolerant of hyperoxic exposure than lipid-unsupplemented cultures focused on the marked changes in fatty acid composition of the cells grown in the two culture conditions and the changes that occurred after hyperoxic exposure (2). Rabbit TE cells cultured in lipid-supplemented media had fatty acid profiles that resembled those of native airway epithelium, whereas unsupplemented cells had lost more than 95% of the arachidonic acid and approximately 80% of the linoleic acid found in freshly isolated TE cells (1, 2). Proposed mechanisms by which lipid-supplemented TE cells with "normal" polyunsaturated fatty acid content were protected from hyperoxic injury included differences in the susceptibility of constituent membrane fatty acids to lipid peroxidation and/or "expendable" pools of nonmembrane-associated lipids acting as free radical scavengers (20, 21). The present studies suggest that in addition to these proposed mechanisms, the increased capacity of lipid-supplemented TE cells to generate PGE₂ also protects these cells from hyperoxic injury. However, the mechanism by which PGE₂ ameliorates hyperoxic injury is uncertain. Exogenous PGE₂ has been shown to protect isolated guinea pig gastric chief cells from ethanol injury by activation of the diacylglycerol/protein kinase C signal pathway (22).

PGE₂ is the predominant cyclooxygenase metabolite generated by mammalian airway epithelial cells (23–26). Several epithelial cell functions, such as ciliary beat frequency and vectorial ion transport, are modulated by PGE₂ (27, 28), and PGE₂ produced by epithelial cells may be an endogenous bronchodilator necessary for the maintenance of normal airway smooth muscle tone (29, 30). Exogenously administered PGE₂ has been shown to attenuate pulmonary injury (8, 9), perhaps in part by inhibiting neutrophil recruitment and activation (31, 32). Our studies sug-

gest that endogenously produced PGE₂ has a role in protecting the airway epithelium from hyperoxic injury. We speculate that in clinical conditions of essential fatty acid deficiency, such as in low birth weight infants deprived of dietary lipids (33) or in cystic fibrosis patients with pancreatic insufficiency (34, 35), decreased PGE₂ synthesis by airway epithelial cells and loss of the bronchodilator and antiinflammatory effects provided by this prostaglandin could lead to increased susceptibility to airway injury from hyperoxia or other airway insults. In uncompromised subjects, decreased airway epithelial cell PGE₂ production induced by hyperoxia might hinder the modulation of airway injury.

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