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Environmental Influences on Uptake of Serotonin and Other Amines

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Lungs accumulate 5-hydroxytryptamine (serotonin, 5-HT) from the perfusate by a sodium-dependent, energy-requiring, saturable process. The rate-limiting step for uptake is the transport of 5-HT and not its subsequent metabolism to 5-hydroxyindoleacetic acid. Autoradiographic studies indicate that the pulmonary endothelium is the cellular site of uptake. The effect of hyperoxia on lung clearance of 5-HT was studied with isolated perfused and ventilated lungs from rats that were previously exposed to hyperoxia. Lungs were perfused with recirculating electrolyte solution and initial [5-HT] of 0.25μM. The calculated fractional 5-HT clearance (fraction of 5-HT removed in a single pass) was 0.77 ± 0.02 (mean ± SE: $n = 44$) for control rats. Mean fractional clearance decreased by 20% in rats exposed to 1 atm O_2 for 18 hr and 30% after 4 atmospheres absolute (ata) O_2 for 1 hr ($p < 0.05$). The effects of O_2 at 4 ata were in part reversed by exposure to air for 3.5 hr and in part prevented by injection of superoxide dismutase (60 nmole/kg body weight). This degree of O_2 exposure at either 1 or 4 ata had no effect on lung content of adenine nucleotides or the distribution of ^{3}H-5-HT on autoradiography. Rats maintained for 6 weeks on a vitamin E-deficient diet showed an increased effect of hyperoxia on 5-HT clearance and did not show reversal of changes after 24 hr of air breathing. The results indicate that exposure to elevated p_{O_2} results in reversible depression of pulmonary 5-HT clearance that is potentiated by vitamin E deficiency. This suggests alteration of pulmonary endothelial membrane transport properties due to O_2 toxicity.

Clearance of Serotonin and Other Amines by the Lung

It is well-established that the lungs of mammalian species remove 5-hydroxytryptamine (5-HT or serotonin) from the pulmonary circulation and metabolize it to 5-hydroxyindoleacetic acid (5-HIAA) (*1-6*). This process of uptake and metabolism serves to inactivate circulating serotonin, and may be important in regulating the systemic arterial concentration of this powerful vasoconstrictor. Although other organs may also remove serotonin from the perfusate, the role of the lung may be of major importance because this organ consists of a vast capillary bed which receives the entire cardiac output. The site of serotonin uptake in the pulmonary capillaries has been localized to the pulmonary endothelial cell (*7, 8*).

Several lines of evidence indicate that capillary endothelial uptake of serotonin is carrier-mediated, and is very likely an active transport process. First, measurement of 5-HT uptake as a function of perfusate concentration suggests a saturable process (*4, 7, 9*). Second, uptake requires the presence of Na^+ in the perfusate (*4*) and is inhibited by ouabain (*4, 10*), suggesting involvement of the Na^+ K^+ activated ATPase. Third, uptake is inhibited by hypothermia (*3, 4, 7*), anoxia (*4, 6*), cyanide (*6*) and absence of a metabolizable substrate (*6*), indicating the requirement for metabolically generated energy. The use of 2-dexoyglucose illustrates the requirement for metabolic energy. This agent, which serves as an ATP trap and inhibitor of glucose metabolism, leads to depression of serotonin uptake that can be reversed by adding a metabolizable substrate (*11*). Finally, uptake of serotonin can be blocked by inhibitors of amine transport such as imipramine, chloropromazine and cocaine (*4, 6, 12*). Definitive proof that transport occurs by active transport re-

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quires demonstration of uptake against a concentration gradient, but this has not yet been accomplished because of the difficulty of demonstrating free, i.e., unbound, intracellular serotonin.

The rate-limiting step for serotonin clearance from the perfusate is the uptake process rather than the subsequent metabolism of 5-HT to 5-HIAA. Thus the presence of a monoamine oxidase inhibitor such as iproniazid does not affect the rate of uptake of 5-HT although conversion to 5-HIAA is markedly depressed (*1-4, 6*). On the other hand, a possible effect of prolonged MAO inhibition on serotonin uptake has not been evaluated.

Other amines are also removed from the circulation by lung endothelium although uptake mechanisms may vary. Norepinephrine, like serotonin, is removed by a carrier-mediated process of pulmonary endothelium (*2, 7, 10*) that can be differentiated pharmacologically from the 5-HT carrier (*12*). Imipramine, which is not transported intracellularly and does not undergo metabolic transformation, is removed through specific binding to the cell membrane (*13*).

Studies of serotonin uptake from this laboratory with isolated guinea pig lungs are shown in Figures 1 and 2. Similar results were obtained with isolated rat lungs, although the normal rates of serotonin clearance are slightly higher with this latter species. Rats were used for studies of oxygen toxicity, since the reaction of their lungs to oxygen is better defined and their lungs are easier to perfuse.

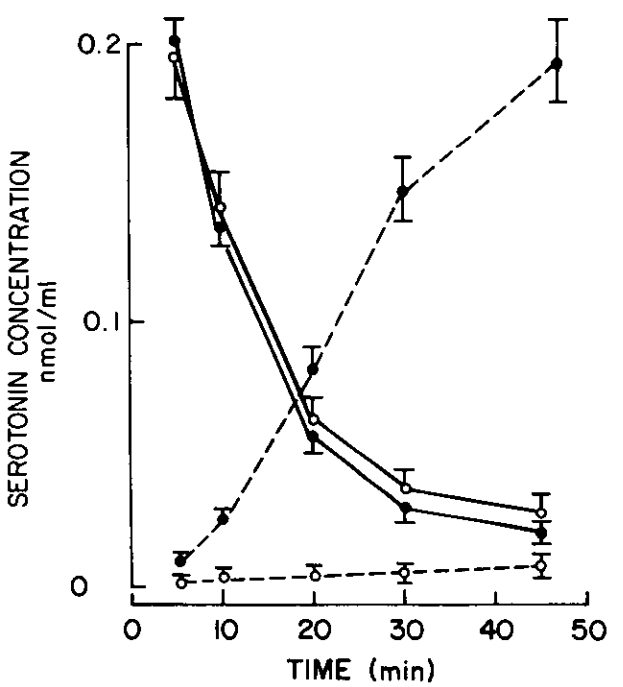

FIGURE 1. Concentrations of (—) serotonin and (- -) 5-hydroxyindoleacetic acid (dashed lines) are plotted versus time of recirculating perfusion of isolated guinea pig lung with ^{14}C-serotonin: (●) in the absence or (○) presence of 0.1*mM* iproniazide. Results are means ± SE for three experiments under each condition.

Pulmonary Oxygen Toxicity

Exposure of animals to oxygen partial pressures above 0.5 atmospheres absolute (ata), i.e., approximately 350 mm Hg, results in their death with a time course that is a hyperbolic function of inspired oxygen (*14, 15*). With O_2 partial pressures up to approximately 2.5 ata, the lungs are the predominant site of injury. Electron microscopic studies of oxygen-damaged lungs have shown lung cell injury with destruction most marked in the pulmonary endothelium (*5, 16, 17*). This information provided the background to investigate the influence of hyperoxia on the subsequent ability of lungs to remove serotonin and other amines from the pulmonary circulation. The goal was to define the early manifestations of hyperoxic damage to pulmonary endothelium.

Effects of Oxygen Exposure on Clearance of Serotonin and Other Amines

Specific pathogen-free rats weighing 250-300 g were exposed to O_2 for varying durations at either 1 ata in an environmental chamber or 4 ata in a hyperbaric pressure chamber. The use of specific pathogen-free rats is important to minimize the complication of possible respiratory tract infections. Sexually mature animals were chosen for study because of the known decreased susceptibility of immature rats to the toxic effects of O_2 (*18*). Ambient CO_2 concentrations in the chamber were maintained below 3 mm Hg with CO_2 absorbent. Since rats exposed to O_2 do not maintain food intake, food was withheld from both control and experimental animals alike to minimize the influence of this variable. Drinking water was provided ad libitum. Some animals were maintained on a vitamin E-deficient diet for approximately 6 weeks before O_2 exposure. Vitamin E deficiency in these rats was confirmed with the dialuric acid erythrocyte hemolysis test (*19*). Rats maintained on the vitamin E-deficient diet gained weight normally.

Following exposure of rats, lungs were removed and evaluated in an isolated lung perfusion system for their ability to remove serotonin, norepinephrine, or imipramine from the perfusate. Serotonin

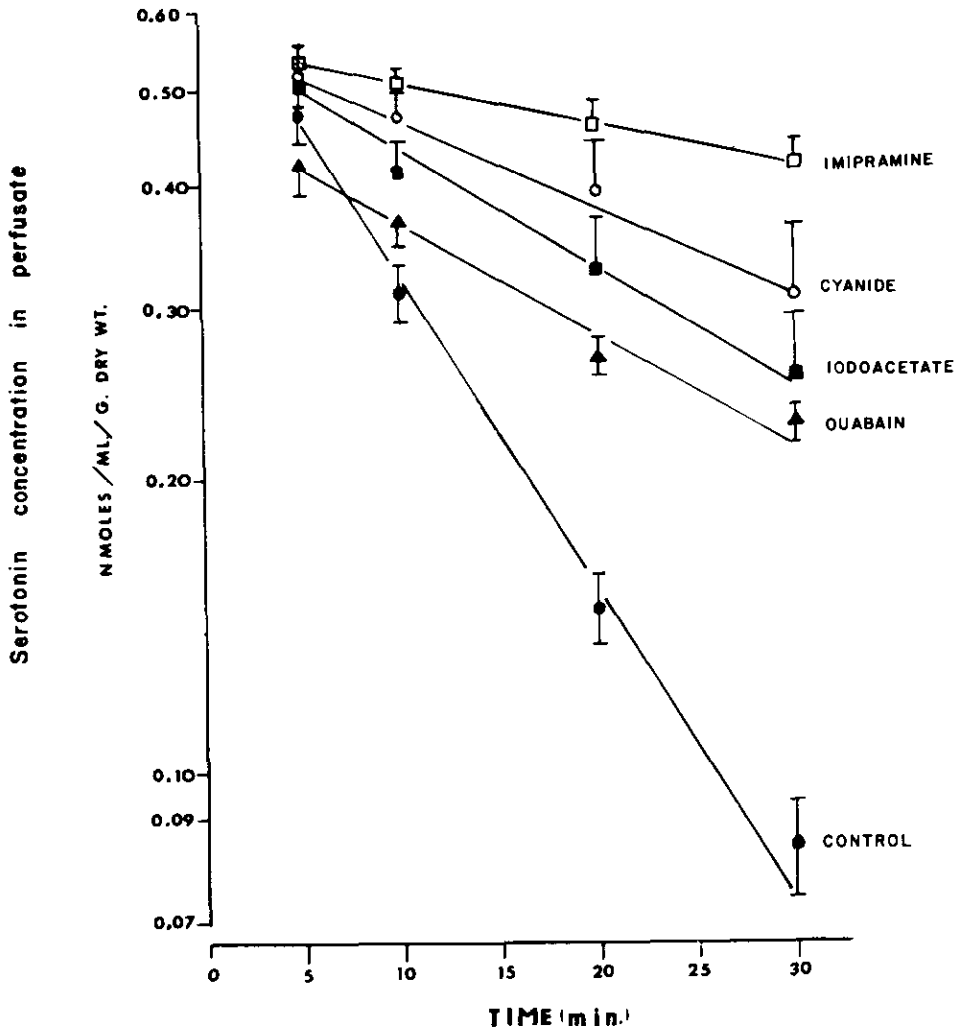

FIGURE 2. Semilogarithmic plot of the serotonin concentration in pulmonary perfusate versus time of perfusion of isolated guinea pig lungs in a recirculating system. Serotonin was measured after separation from its metabolic products by column chromatography. The inhibitors used were 0.1*mM* imipramine, 1*mM* KCN, 1*mM* iodoacetate, and 0.01*mM* ouabain. Results are the means ± SE for 13 control experiments and 3-5 experiments with each inhibitor.

uptake was evaluated in a recirculating system (*20*). The first order rate constant was calculated from the semilogarithmic decrease of perfusate serotonin concentration as a function of time; the fractional clearance was calculated from the rate constant and the average recirculation time (*6*). Uptake of norepinephrine and imipramine was evaluated using "once-through" perfusion. Clearance of these amines was calculated from the arterial-venous difference in concentration and the rate of perfusion (*21*). Assay for each of the amines in the perfusate was done by radiolabel counting following separation of the amine from its metabolic products.

Effects of Oxygen Exposure on Serotonin Clearance

Normal Rats

Fractional clearance of serotonin in control animals that were not exposed to oxygen was approximately 0.80, indicating that approximately 80% of the serotonin presented to the lung was cleared during a single passage through the pulmonary circulation. Mean serotonin clearance in lungs from rats exposed to oxygen was decreased by 5% after 4 hr O_2, 12% after 12 hr O_2, 25% after 18 hr O_2, and 35%

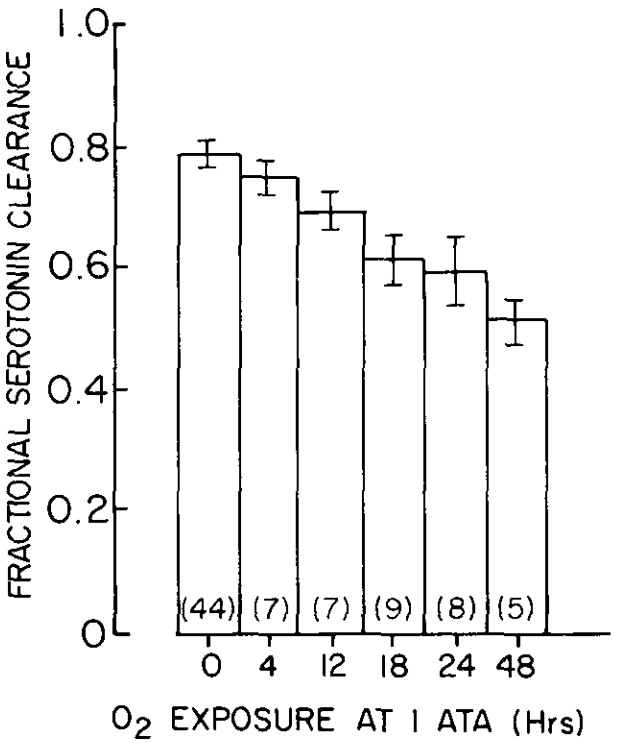

FIGURE 3. Serotonin clearance by lungs from normal rats exposed to oxygen at 1 atmosphere absolute (ata). Results are the means ± SE for the number of experiments indicated at the bottom of each block.

after 48 hr O_2 (Fig. 3). The effect of O_2 on serotonin clearance was an approximate hyperbolic function of exposure time with an estimated plateau value of 40-50% depression of clearance. These results suggest that the ability of the lungs to remove serotonin from the perfusate was depressed within the initial 12 hr of oxygen exposure.

Hyperbaric oxygen at 4 ata greatly accelerated the depression of serotonin clearance. After 1 hr of hyperbaric exposure, clearance was depressed by 30% (Fig. 4), which was approximately equivalent to the effect of 1 ata O_2 for 24 hr.

Vitamin E-Deficient Rats

Vitamin E-deficient rats demonstrated increased susceptibility to the effects of oxygen on pulmonary clearance of serotonin. With O_2 at 1 ata, 5-HT clearance was depressed by 45% after 12 hr of exposure. This exceeded the effect of 48 hr O_2 exposure on normal animals (Fig. 5). The increased susceptibility to O_2 of vitamin E deficient rats was also seen with hyperbaric exposure. Serotonin clearance in vitamin E deficient rats was depressed by approximately 30% after 45 mins and 45% after 60 mins of exposure (Fig. 4). Rats repleted with vitamin E by intraperitoneal injection (1 mg/kg twice weekly) or supplementation of drinking water responded to O_2 at 1 ata similarly to normal diet rats. There was no apparent protection against hyperoxia by these pharmacologic doses of vitamin E (*19*).

Protection Against the Effects of Oxygen

The use of hyperbaric exposure provided a convenient model for evaluating the effect of possible protective agents on the pulmonary response to hyperoxia since only short exposures were required. Rats were treated with a single dose of possible protective agents intraperitoneally 45 min prior to exposure (*22*). GSH (reduced glutathione) (16 mmole/kg body weight) or sodium succinate (12 mmole/kg body weight) had no effect on subsequent depression of serotonin clearance by hyperbaric oxygen exposure (Fig. 4). It should be noted that these rats were fed prior to administration of succinate although fasting is required to prolong survival by this agent (*23*). Pretreatment of animals with superoxide dismustase (Palosein, Diagnostic Data Inc., Mountain View, Calif.) (60 nmole/kg body weight) partially prevented the subsequent effects of

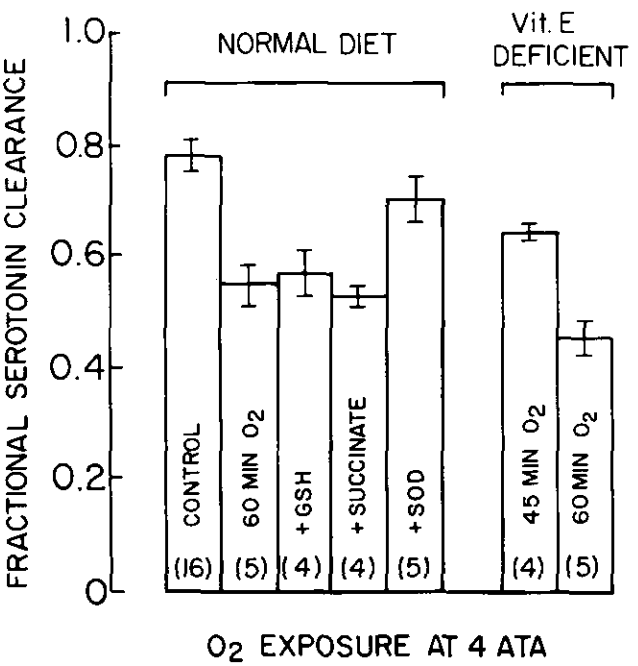

FIGURE 4. Serotonin clearance by lungs of rats exposed to O_2 at 4 ata. Control animals were maintained in room air. Animals maintained on a normal diet were exposed to O_2 for 1 hr. Vitamin E-deficient animals were exposed to O_2 for 45 or 60 min as indicated. Individual groups of animals were pretreated by intraperitoneal injection of GSH (reduced glutathione), succinate, or superoxide dismutase.

hyperbaric oxygen on serotonin clearance (Fig. 4). In five animals pretreated with superoxide dismutase, mean serotonin clearance was depressed by only 11%, compared with 30% decrease in saline-injected control animals.

Recovery From Hyperoxic Lung Damage

The hyperbaric exposure model was also used to study recovery from oxygen-induced depression of serotonin clearance (*24*). Following O_2 exposure at 4 ata, animals breathed room air for varying periods before measurement of serotonin clearance. In animals fed with a normal diet, serotonin clearance was partially restored to control values after 1.5 hr of air breathing and was approximately 90% of control after 3 hr. On the other hand, recovery of vitamin E deficient animals from O_2 toxicity was much delayed. Vitamin E deficient animals showed essentially no recovery of serotonin clearance by 3 hr after O_2 exposure and even 24 hr post-exposure of air breathing, serotonin clearance was 30% below control values. This data suggests that vitamin E not only protects against hyperoxic depression of serotonin clearance but is also required for recovery from the toxic effects of O_2.

Effects of O_2 Exposure On Clearance Of Norepinephrine And Imipramine

Clearance of norepinephrine by lungs was also depressed following hyperoxia (*21*). The relationship between duration of oxygen exposure at 1 ata and depression of norepinephrine clearance essentially paralleled the findings with serotonin (Table 1). Norepinephrine clearance was depressed by 39% after 24 hr and by 51% after 48 hr of O_2. On the other hand, imipramine clearance (*21, 25*) was unaffected by oxygen exposure for up to 48 hr (Table 1).

Pulmonary Physiologic, Morphologic, and Metabolic Effects of Hyperoxia

The above studies indicated that depression of serotonin uptake was an early and reversible manifestation of pulmonary oxygen toxicity that was potentiated by vitamin E deficiency. Additional studies indicated that depression of serotonin uptake occurred before other evidence of morphologic, physiologic or biochemical derangement of the lungs. The normal rats exposed to oxygen at 1 ata for up to 48 hr or 4 ata for 1 hr had no signs of respiratory distress, and their lungs appeared grossly normal. The hyperbaric oxygen exposure was just below the convulsive threshold but an occasional rat did develop generalized seizures and was not used for further studies. Vitamin E-deficient rats developed respiratory distress after 18 hr exposure to 1 ata or 1 hr exposure to 4 ata of oxygen.

Physiologic Changes In Lungs From O_2 Exposed Rats

Perfusion pressure at constant flow rate and ventilation pressure at constant tidal volume were measured in the isolated lung during lung perfusion in order to evaluate lung mechanical and vascular properties. Similar values for these pressure measurements were obtained for control and oxygen-exposed normal or vitamin E deficient animals. To evaluate the distribution of perfusate to the lung, ^{85}Sr-labeled microspheres (15 μm diameter) were infused into the pulmonary artery (*19*). The distribu-

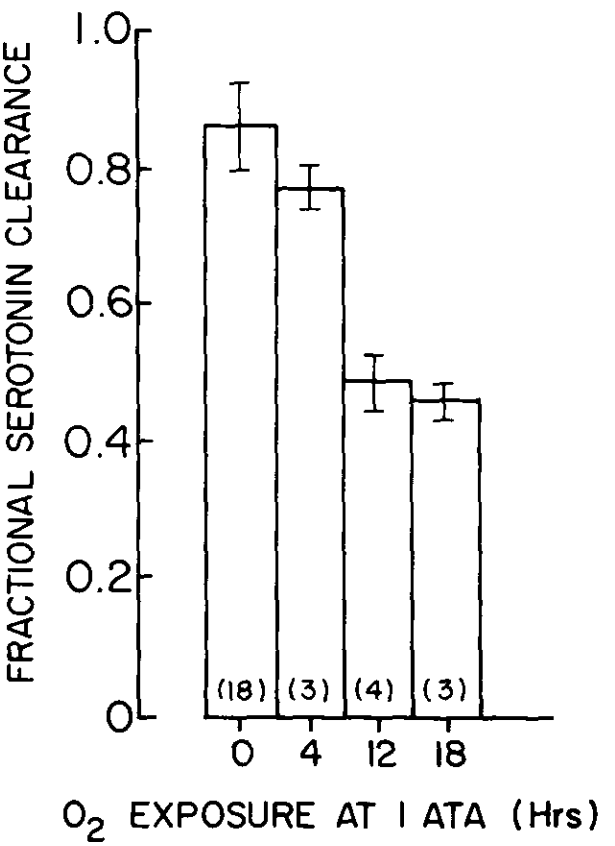

FIGURE 5. Serotonin clearance by lungs from vitamin E deficient rats exposed to oxygen at 1 ata for varying duration. Results are mean ± SE for the number of experiments indicated at the bottom of each block.

tion of radioactivity per unit tissue was slightly greater in the lower compared to upper lobes, but was similar in control and O_2-exposed animals. The ratio of lung dry to wet wt and the end of perfusion was 0.17-0.18 for both control and oxygen-exposed animals. These are normal values for dry to wet weight ratio of rat lungs perfused with electrolyte solutions indicating the absence of significant fluid accumulation.

The results suggest that derangement of lung mechanics, altered pulmonary perfusion, or lung edema was not associated with the decreased serotonin clearance that occurred with O_2 exposure.

Metabolic Effects Of Hyperoxia

Lung metabolism as a function of oxygen exposure was evaluated by measuring lung tissue adenine nucleotides and the rates of lung lactate and pyruvate production (*26*). After 1 hr perfusion, lung ATP and ATP/ADP were maintained at a high level with no significant difference between control and O_2-exposed rats (Table 2). The rates of production of lactate and pyruvate by the isolated perfused lung and the lactate to pyruvate ratio were unaffected by exposure of rats to oxygen for 18 or 24 hr (*26*). However, lungs from rats exposed to oxygen for 48 hr demonstrated 60% increase in lactate production with an approximate doubling of the lactate to pyruvate ratio. These studies indicate that, at least through 24 hr of O_2 exposure, there was no alteration of lung glycolysis or energy balance, suggesting that interference with energy generation metabolism was not responsible for altered amine clearance. On the other hand, the possibility of metabolic changes specifically localized to lung endothelial cells cannot be excluded.

Table 1. Effect of O_2 exposure on lung clearance of amines.

O_2 (at 1 ata)	Norepinephrine, *nmole/min-g* dry[a]	Clearance, % of *mean* control	Imipramine, *nmole/min-g* dry[a]	Clearance, % of *mean* control
Control	2.76 ± 0.07 (n = 18)	100	7.52 ± 0.05 (*n* = 12)	100
12 hr	2.59 ± 0.22 (*n* = 8)	94	7.55 ± 0.10 (*n* = 5)	100
24 hr	1.69 ± 0.14 (*n* = 8)	61	7.53 ± 0.14 (*n* = 6)	100
48 hr	1.35 ± 0.21 (n = 6)	49	7.49 ± 0.07 (*n* = 6)	100

[a]Values are mean ± SE.

Electron Microscopy And Autoradiography

In order to study the effect of O_2 on localization of 5-HT, the lungs from two rats exposed to O_2 at 4 ata for 1 hr and one rat exposed to O_2 at 1 ata for 48 hr were perfused with ^{3}H-serotonin in the presence of iproniazide to prevent 5-HT metabolism. Examination of these lungs with the electron microscope failed to reveal ultrastructural abnormalities at the level of the alveolar septum. On autoradiography of the O_2 exposed lungs, silver grains were localized predominately to the endothelial cells (Fig. 6 and Table 3). These results indicate that this degree of hyperoxia did not cause ultrastructural damage to the lung and that the accumulation of serotonin even with oxygen-exposed animals was still predominately in the endothelial compartment.

Table 2. Effect of O_2 exposure on adenine nucleotide content of rat lungs.

	n	ATP, *μmole/g dry*[a]	ATP/ADP, *μmole/g dry*[a]
Control	3	12.8 ± 0.1	7.2 ± 0.7
O_2 at 1 ata			
24 hr	3	12.2 ± 1.0	8.1 ± 0.4
48 hr	3	11.8 ± 0.6	7.6 ± 1.1
Control	7	10.5 ± 0.4	8.6 ± 0.7
O_2 at 4 ata, 1 hr	4	9.8 ± 0.4	8.0 ± 0.5

[a]Results are mean ± SE.

Table 3. ^{3}H localization in autoradiographs of rat lung following perfusion with ^{3}H-5-hydroxytryptamine.

	Grains/μ^2[a]		Observed/expected[b]	
O_2 exposure	Endothelium	Other	Endothelium	Other
O_2, 4 ata, 1 hr	0.09	0.02	1.7	0.3
O_2, 4 ata, 1 hr	0.11	0.03	1.6	0.4
O_2, 1 ata, 48 hr	0.13	0.03	1.6	0.4

[a]Results are mean values based on 10-15 micrographs.
[b]By χ^2 analysis.

Mechanisms of Depression of Amine Uptake

Clearance of serotonin and norepinephrine was inhibited at an early stage in the development of pulmonary oxygen toxicity. The evidence that O_2 toxicity was at an early stage was the failure to demonstrate pulmonary derangement by morphologic,

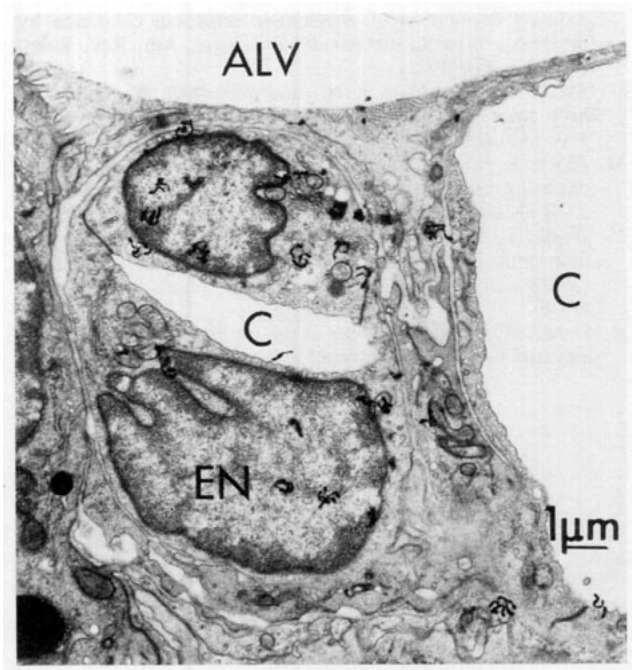

FIGURE 6. Electron microscope autoradiogram of the lung from a rat exposed to 4 ata O_2 for 1 hr and subsequently perfused with ^{3}H-5 HT in the presence of iproniazide. Developed silver grains have accumulated predominantly over the capillary endothelium (EN). There are no anatomic alterations in the constituents of the alveolar-capillary membrane attributable to oxygen exposure. Tubular myelin and amorphous material probably representing surfactant are present at the interface between alveolar air and alveolar epithelium. Sections were stained with uranyl acetate-lead hydroxide. ALV=alveolar space; C=capillary space. × 6300.

physiologic, or metabolic criteria. On the other hand, removal of imipramine was not depressed at this stage of oxygen exposure. This differential effect on clearance can be explained by the differences in normal handling of the amines. Serotonin and norepinephrine are probably transported actively by the pulmonary endothelial cell while imipramine is cleared by passive binding. Therefore, we conclude that oxygen may exert its effect on the pulmonary endothelial cell membrane and thereby interfere with the active transport process for circulating amines. Since uptake of both serotonin and norepinephrine was affected, the toxic effect of O_2 either involved more than one carrier or some basic mechanism common to the transport of both amines. The results with metabolic studies suggests that the common mechanism was not alteration of energy supply. One possibility is an effect of O_2 on the membrane Na^+-K^+ATPase. The answer to this problem awaits further definition of the precise mechanisms involved in amine transport.

Summary and Conclusions

Exposure to elevated partial pressure of oxygen results in early and reversible depression of active amine (serotonin and norepinephrine) transport by the rat lung. A possible mechanism is that O_2 exerts a toxic effect on the pulmonary endothelial cell membrane. The findings may provide a convenient metabolic marker for the early toxic effects of oxygen on the lung. The significance of decreased amine clearance in the pathogenesis of the systemic manifestations of oxygen poisoning remains to be evaluated.

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