MINIREVIEW

Superoxide Dismutase and Pulmonary Oxygen Toxicity (43600A)

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Abstract. **Three forms of superoxide dismutase (SOD) exist in the lung: CuZnSOD, MnSOD and extracellular SOD. Evidence suggests that both CuZnSOD and MnSOD are important in pulmonary defense against oxygen toxicity. Enhancement of pulmonary levels of CuZnSOD by transgenic overexpression of CuZnSOD, or tracheal insufflation of liposome-encapsulated or polyethylene glycol-conjugated CuZnSOD, protects animals against oxygen toxicity. Likewise, transgenic overexpression of MnSOD, or induction of endogenous MnSOD by endotoxin, tumor necrosis factor, or interleukin 1, also protects animals against oxygen toxicity. The role of extracellular SOD in the pulmonary defense against oxygen toxicity is not clear.** [P.S.E.B.M. 1993, Vol 203]

A significant fraction of biologic oxygen reduction, enzymatic or nonenzymatic, occurs via the pathway of univalent reduction resulting in the generation of superoxide anion (O_2^-). Superoxide anion is a reactive oxygen free radical. It is also capable of producing potent oxidants, e.g., hydrogen peroxide (H_2O_2) (via enzymatic or spontaneous dismutation [Reaction 1]), or hydroxyl radical ($OH^\bullet$) (via Haber-Weiss reaction [Reaction 2]) (1):

$$O^\bullet + O_2 + 2H^+ \longrightarrow H_2O_2 + O_2 \longrightarrow \text{Reaction 1} \quad [1]$$

$$O^\bullet + H_2O_2 \xrightarrow{Fe^{3+}} OH^- + OH^\bullet + O_2 \text{—Reaction 2} \quad [2]$$

The production of these reactive oxygen species (O_2^-, H_2O_2, and $OH^\bullet$) is markedly accentuated under hyperoxic conditions leading to tissue (especially pulmonary) injury (2). Considerable evidence suggests that during the hyperoxic exposure, reactive oxygen species are produced both intracellularly by lung parenchymal cells and extracellularly by infiltrating neutrophils (3–5).

Superoxide dismutase (SOD) is a family of enzymes that catalyze the dismutation of O_2^- to H_2O_2 and O_2 (Reaction 1). By rapidly eliminating O_2^-, SOD reduces the tissue concentrations of O_2^- and $OH^\bullet$ (Reaction 2). Thus, if lung tissue contains sufficient quantities of catalase and glutathione (GSH) peroxidase to dispose H_2O_2, augmentation of pulmonary SOD has the potential to protect animals against pulmonary oxygen toxicity. This minireview summarizes our current understanding of the role of SOD in the protection against pulmonary oxygen toxicity.

Superoxide Dismutase

Three forms of SOD, with distinct distribution and characterized by their metal components, exist in eukaryotes: CuZnSOD, MnSOD, and extracellular SOD which also contains Cu and Zn (1, 6). Intracellular CuZnSOD constitutes approximately 85%–90% of the total cellular SOD activity. Although it is usually regarded as a cytosolic enzyme, recent evidence suggests that the majority of this enzyme may actually be located in peroxisomes (7). MnSOD, which constitutes approx-

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imately 10%–15% of the total cellular SOD activity, is located in mitochondria. It is an inducible enzyme; induction of MnSOD in eukaryotes has been demonstrated following exposure to irradiation (8), or hyperoxia (9), or following treatment with paraquat (10), tumor necrosis factor (TNF) (11–13), interleukin 1 (IL-1) (12, 14), or endotoxin (12, 15). Extracellular SOD is a Cu,Zn-containing enzyme distinct from intracellular CuZnSOD. It is the dominant SOD isoenzyme in the plasma; however, its tissue content is much lower than that of CuZnSOD or MnSOD (6). Little is known about the biologic function of extracellular SOD, including its role in the defense against oxygen toxicity.

CuZnSOD and Oxygen Toxicity

Considerable evidence supports the importance of cytosolic or peroxisomal CuZnSOD in the pulmonary defense against oxygen toxicity. A boy with partial monosomy 21 and diminished CuZnSOD activity (in humans, the gene encoding for CuZnSOD is located on chromosome 21) was found to have a markedly increased sensitivity to pulmonary oxygen toxicity, which suggests that normal levels of CuZnSOD are essential for the pulmonary defense against oxygen toxicity (16). Survival advantage was noted in young (2.5 months old) but not old (5 months old), female but not male, mice with transgenic overexpression of pulmonary CuZnSOD, exposed to 100% O_2 at a reduced atmospheric pressure (630 torr), but not at the sea level atmospheric pressure (760 torr) (17). It is not clear why the protective effect of increased pulmonary CuZnSOD was noted only in a subgroup of young, female, transgenic mice under reduced atmospheric pressure.

Exposure of rats to a sublethal dose of normobaric O_2 (85% or 90%) for 7 days results in a significant increase in pulmonary levels of CuZnSOD, MnSOD, catalase, and GSH peroxidase (18, 19). These antioxidant enzyme-augmented animals become tolerant to a lethal dose (>95%) of O_2. Likewise, rats pre-exposed to hypoxia (10% O_2) for 3 days also become tolerant to lethal hyperoxia (20). This hypoxia-induced oxygen tolerance is associated with increased pulmonary levels of total SOD, catalase, and GSH peroxidase. Neonatal rats, mice, and rabbits are more resistant to lethal doses of O_2 than their adult counterparts (21–23). This is due in part to these neonatal animals' ability to increase pulmonary levels of total SOD, catalase, and GSH peroxidase within 24 hr of O_2 exposure. Since antioxidant enzymes other than pulmonary CuZnSOD are also increased under the above conditions, increased level of pulmonary CuZnSOD may not be solely responsible for the increased tolerance to pulmonary oxygen toxicity.

Considerable effort has been made in recent years to enhance oxygen tolerance by increasing pulmonary SOD activity. Because of the extremely short plasma half-life (a few minutes) and poor cellular uptake of CuZnSOD, administration of CuZnSOD by intravenous injection or aerosol inhalation does not protect animals against oxygen toxicity (24, 25). Liposome encapsulation or polyethylene glycol (PEG) conjugation of CuZnSOD has been used successfully to prolong its plasma half-life and increase cellular uptake of the enzyme (25–27). Tracheal insufflation of liposome-encapsulated CuZnSOD (28) or PEG-CuZnSOD (29) protects rats against oxygen toxicity. However, intravenous or intraperitoneal administration of liposome-encapsulated CuZnSOD or PEG-CuZnSOD does not protect animals against oxygen toxicity, unless they are co-administered with liposome-encapsulated catalase or PEG-catalase, respectively (27, 30). This may be due in part to the fact that at a similar dosage, tracheal insufflation of PEG-CuZnSOD increases pulmonary SOD activity to a much greater extent than intravenous injection (29).

Intraperitoneal administration of a sublethal dose of endotoxin (500 μg/kg) to rats exposed to hyperoxia also results in increased lung total SOD activity, decreased O_2-induced lung damage, and an improved survival rate (31). The endotoxin- and hyperoxia-induced increase in pulmonary SOD activity was thought to be due to an increase in CuZnSOD, since the increased pulmonary SOD activity could be abolished by pretreatment with diethyldithiocarbamate, a Cu-chelating agent and an inhibitor of CuZnSOD (32). Furthermore, levels of pulmonary CuZnSOD mRNA and specific protein were also found to be slightly increased in endotoxin-treated and hyperoxia-exposed rats, suggesting the possible role of CuZnSOD in the protection against oxygen toxicity (33, 34). However, levels of pulmonary MnSOD mRNA, specific (immunoreactive) protein, or enzyme activity were not measured in the above studies. In addition, diethyldithiocarbamate is a nonspecific inhibitor and may have effects other than inhibition of CuZnSOD to account for the observed response. A recent abstract from the same group of investigators (35) reported that endotoxin-induced oxygen tolerance was not associated with an increase in CuZnSOD. Instead, it was associated with a marked increase in levels of pulmonary MnSOD mRNA and enzyme activity.

MnSOD and Oxygen Toxicity

Despite its strategic location in mitochondria, a major site of O_2^- production under hyperoxic conditions (3), the potential role of MnSOD in the pulmonary defense against oxygen toxicity has not attracted much attention. This is in part due to the fact that MnSOD constitutes a minor fraction of the total pulmonary SOD activity and its activity is difficult to measure. Most previous studies have only measured total pulmonary SOD activity, which may overlook a

significant alteration of MnSOD activity. The above-mentioned increase in pulmonary SOD activity within 24 hr of O_2 exposure in neonatal rats is accounted for solely by an increase in MnSOD activity (23). The recent demonstration that endotoxin, TNF, or IL-1 selectively induces MnSOD mRNA, leading to increased MnSOD specific protein and enzyme activity, without affecting the levels of other antioxidant enzymes, including CuZnSOD, catalase, and GSH peroxidase (11–15), has called attention to the potential role of pulmonary MnSOD in the protection against oxygen toxicity.

Tracheal insufflation, but not intraperitoneal injection, of a single dose (e.g., 5 μg) of TNF or IL-1 attenuates O_2-induced pulmonary injury and prolongs the survival of rats exposed to 100% O_2 (36, 37). TNF- or IL-1-insufflation-induced protection against oxygen toxicity is associated with a selective enhancement of pulmonary MnSOD mRNA, specific protein, and enzyme activity at 2.3 days (55 hr) after O_2 exposure, when control rats start to die of oxygen toxicity (36–39). Exposure of control rats to 100% O_2 also results in a marked enhancement of pulmonary MnSOD mRNA. However, this is not associated with an increase in pulmonary MnSOD specific protein or enzyme activity. Instead, at 2.3 days after O_2 exposure, the levels of pulmonary MnSOD specific protein and enzyme activity are reduced by approximately 30% (36–39). TNF and IL-1 act synergistically in protecting rats against oxygen toxicity and in enhancing endothelial cell MnSOD, but not CuZnSOD, mRNA levels. Interleukin 6, which provides no protective effect in rats against oxygen toxicity and has no apparent effect on endothelial cell MnSOD mRNA levels, markedly enhances TNF- and IL-1-induced increases in endothelial cell MnSOD mRNA levels and in oxygen tolerance in rats (40). Similarly, D factor (differentiation-inducing factor) and growth hormone enhance the TNF-induced increase in pulmonary MnSOD mRNA, they also enhance TNF- induced oxygen tolerance (41).

These results support an important role of MnSOD in the pulmonary defense against oxygen toxicity. For example, failure of hyperoxia-exposed rats to increase pulmonary MnSOD protein and enzyme activity in the presence of an elevated level of MnSOD mRNA may contribute to the pathogenesis of pulmonary oxygen toxicity, and enhancement of pulmonary MnSOD plays an important role in the cytokine-induced protection against oxygen toxicity. In a recent abstract, Massaro *et al.* (35) also reported that exposure of rats to >95% O_2 resulted in a markedly elevated level of pulmonary MnSOD mRNA, while the activity of pulmonary MnSOD was reduced by approximately 50%. Furthermore, endotoxin treatment resulted in a selective enhancement of pulmonary MnSOD mRNA and enzyme activity in O_2-exposed rats, which suggests that enhanced pulmonary MnSOD, but not other antioxidant enzymes including CuZnSOD, plays an important role in the endotoxin-induced oxygen tolerance (35). Protection of mice against oxygen toxicity by TNF is also associated with an induction of pulmonary MnSOD mRNA (42). Further support of the importance of MnSOD in the host defense against oxygen toxicity comes from a recent study of transgenic mice in which expression of human MnSOD mRNA in Type II alveolar and non-ciliated bronchiolar epithelial cells confers protection against pulmonary oxygen toxicity (43).

The mechanism by which endotoxin, cytokines, or hyperoxia enhances MnSOD mRNA has been studied in cultured cells and lung tissues. Visner *et al.* (12, 44) reported that endotoxin-induced enhancement of MnSOD mRNA levels in rat pulmonary epithelial cells or in porcine pulmonary artery endothelial cells was completely inhibited by the RNA synthesis inhibitor, actinomycin D, which suggests that induction of MnSOD mRNA by endotoxin was regulated at least in part at the transcriptional level. Likewise, induction of MnSOD mRNA by TNF or IL-1 in a number of cell types is dependent upon *de novo* transcription requiring no *de novo* protein synthesis (45, 46). Massaro *et al.* (35) reported that the O_2-induced increase in pulmonary MnSOD mRNA was due to an increase in MnSOD mRNA stability. Furthermore, in endotoxin-treated rats exposed to normoxia, the increased pulmonary MnSOD mRNA level was due to an increased rate of transcription, while in endotoxin-treated rats exposed to hyperoxia, the increased level of pulmonary MnSOD mRNA was due to a combination of increased transcription and increased stability of mRNA.

A number of investigators have questioned the role of pulmonary antioxidant enzymes in endotoxin- or cytokine-induced oxygen tolerance. Hazinski *et al.* (47) reported that intravenous injection of endotoxin protected lambs against O_2-induced pulmonary injury and prolonged their survival. This endotoxin-induced protection against oxygen toxicity was not associated with any increase in pulmonary antioxidant enzymes when control animals were suffering from severe oxygen toxicity. Similar observations were made by White *et al.* (48, 49), who gave a combination of IL-1 and TNF to rats in split doses by intraperitoneal and intravenous injections, and by Berg *et al.* (50), who gave sera containing high levels of TNF and IL-1 from rats pretreated with endotoxin to rats by intravenous injection. All these investigators have concluded that an increase of pulmonary antioxidant enzymes is not necessary for the protection against oxygen toxicity. However, none of these studies has measured pulmonary MnSOD activity; instead, only total lung SOD activities were measured. Because MnSOD constitutes a minor fraction of the total cellular SOD, it is possible that an enhance-

ment of lung MnSOD activity may have been overlooked if one determined only total SOD activity.

Conclusion and Directions for Future Studies

Oxygen is an important therapeutic modality for patients with severe hypoxemia. However, prolonged exposure to a high partial pressure of O_2 causes tissue injury which may exacerbate the existing lung pathology (51). At present there is no practical means of preventing oxygen toxicity. The above Minireview clearly indicates that both CuZnSOD and MnSOD are essential in the pulmonary defense against oxygen toxicity, and that enhancement of pulmonary levels of CuZnSOD or MnSOD, e.g., by administration of exogenous CuZnSOD (liposome encapsulated or PEG conjugated) or induction of endogenous MnSOD, can protect animals against oxygen toxicity. This review also raises some important questions for future investigation. (i) Why do animals respond to O_2 exposure by raising pulmonary MnSOD mRNA, but fail to increase pulmonary MnSOD protein or enzyme activity, and succumb to oxygen toxicity? (ii) What is the cellular distribution of, or cell type(s) responsible for, the increased level of pulmonary MnSOD in cytokine- or endotoxin-treated animals? (iii) What is the mechanism for the preferential protective effect of cytokines, liposome-encapsulated CuZnSOD, or PEG-CuZnSOD when given by tracheal route as compared with intravenous or intraperitoneal injection? What is the role of alveolar macrophages in this regard? There is good reason to believe that continued investigation will eventually lead to the development of practical means of preventing oxygen toxicity.

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