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CO protects against hyperoxic lung injury

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Keywords

Acute respiratory distress syndrome, heme, oxidative stress

Comments

Animal experiments always raise the issue of applicability to humans but given the simplicity of this system it is tempting to extrapolate these results. Inhaled CO as a therapy for ARDS is an intriguing possibility that would appear to warrant serious consideration, though this series of experiments only show that one might prevent lung injury, not necessarily ameliorate the condition once established. Level of evidence: Level III (animals-rats).

Introduction

Heme oxygenase (HO) catalyzes the first and rate limiting step in the degradation of heme to biliverdin IXa, iron and carbon monoxide (CO). Three isoforms of HO exist, HO-1 being highly inducible, HO-2 and HO-3 being constitutive. Heme is the major substrate of HO-1 but it is also strongly induced by some heavy metals, cytokines, hormones, endotoxin, hydrogen peroxide, glutathione depletors, ultraviolet irradiation, hyperoxia and heat shock. This diversity of HO-1 inducers has led to speculation that it may play a vital role in cellular homeostasis besides heme degradation, in particular in the adaptation and/or defence against oxidative stress. The mechanisms by which HO-1 provides protection against oxidative stress are unknown but could be due to CO production. CO toxicity is well known, however there is increasing evidence of its physiological role in both neuronal transmission and regulation of vasomotor tone. There are currently no published data assessing its role in the cellular protection against oxidative stress.

Aims

This study was performed to test the hypothesis that CO mediates the protective effects of HO in an in vivo model of oxidative stress.

Methods

Pathogen-free male rats were employed for all experiments. Groups of animals were subjected to room air (controls), room air plus variable dose CO, 98% oxygen or 98% oxygen plus variable dose CO. Arterial canulas were inserted in all animals for estimation of oxygen tension and carboxyhemoglobin levels. After 56 h exposure a selection of rats from each group underwent pleural aspiration to dryness, then 24 h later, bronchoalveolar lavage (BAL). A selection of each group were subjected to pneumonectomy (presumably post mortem) and histology and immunohistochemistry for apoptosis performed. A further selection from each group were administered with either saline (controls) or tin protoporphyrin (SnPP), a potent selective inhibitor of HO, before the experiment and on a daily basis.

Results

Animals subjected to hyperoxia exhibit similar pathophysiology to that seen in human acute respiratory distress syndrome (ARDS). Rats subjected to 98% oxygen develop lung edema and/or pleural effusions by 56 h, which increase progressively leading to death by 72 h. Rats exposed to 50-500 ppm CO show no difference from controls despite identical arterial oxygen tensions. Rats exposed to 98% oxygen and CO showed tolerance to the hyperoxia in a dose responsive fashion, with 100% of those given 250 or 500 ppm CO surviving 72 h and 80% surviving 100 h. Carboxyhemoglobin levels increased from 6.6% in controls to 11.3% in rats exposed to 250 ppm CO. Volume of pleural effusion and total protein accumulation in the airways (estimated from BAL), both standard and highly reliable markers of hyperoxic lung injury, were dramatically increased in the 98% oxygen group compared to the other three groups, which were identical. Routine histology showed marked lung hemorrhage, edema, alveolar septal thickening, influx of inflammatory cells and fibrin deposition in the 98% oxygen group, whereas the other three groups were identical (ie normal) both macroscopically and microscopically. Co-administration of CO also significantly reduced neutrophil influx (measured from BAL) and lung apoptosis index (from immunohistochemistry). Rats given SnPP at a dose to completely inhibit HO, and then exposed to 98% oxygen, showed a dramatic increase in the size of pleural effusion compared to rats given saline and exposed to hyperoxia. This effect was completely ameliorated when the hyperoxia was co-administered with 250 ppm CO.

Discussion

In this series of experiments 0.005-0.05% CO was administered without deleterious effects and prevented hyperoxia induced lung injury. From unpublished work, CO was lethal to rats at doses above 1%. Of note 0.3% CO is routinely used to assess lung diffusion capacity in humans. Hence inhaled CO at these doses could be safely employed in humans. The inhibitory effects of inhaled CO on neutrophil influx are reproduced in unpublished experiments, where lung injury is induced by lipopolysaccharide

administration, suggesting that this may be a crucial mechanism in the apparent anti-inflammatory action of inhaled CO. Similarly, inhibition of apoptosis by inhaled CO would appear to be of clinical importance, as there is growing evidence that apoptosis is a reliable marker of lung injury. The above experiments indicate but do not confirm that endogenous CO production by HO accounts for the protective effects of HO demonstrated by the authors and other workers. Another relevant observation is that CO avidly binds heme moieties such as guanyl cyclase thereby increasing cGMP levels, thus exerting similar effects to nitric oxide, though it also appears to act by other pathways.

References

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