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Hyperoxia-induced regulation of cough reflex and its effect after antioxidant supplementation

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ABSTRACT

Hyperoxia-induced lung injury is well known in animal and human studies. The respiratory epithelium including sensory nerve endings is a major target for oxidative injury that manifested in lung function changes including cough. On the basis of available information we supposed that hyperoxia alone or in combination with primary lung tissue injury should have a damaging effect on lungs, including the airway nerve endings with the changes in the sensitivity of the central and peripheral neuronal pathways regulating cough. We have previously demonstrated that long-term exposure to 100% oxygen inhibits the cough reflex in cat.

This review article summarizes the effect of hyperoxia on the cough reflex in guinea pig model using different concentrations of oxygen and different time of exposure. We also present information on the potential role of antioxidants in reversal of the detrimental effects of hyperoxia on coughing and additional analysis of experiments from previously published studies were obtained and analysed for the cough reflex sensitivity.

1. Introduction

Long-term oxygen therapy has a vital role in surviving in pulmonary critically ill patients such as chronic obstructive pulmonary disease, diffuse interstitial lung disease, cystic fibrosis or bronchopulmonary dysplasia in the new-born. The goal of oxygen therapy, often in high inspired concentrations, is to correct hypoxemia and prevent tissue hypoxia, thus increasing survival and improving quality of life (Chen et al., 1995; Tarpy and Celli, 1995). The concept of oxygen as a therapeutic agent was introduced in 1920s by Alvin Barach (Barach, 1922). Although oxygen supplementation has a beneficial effect, on the other hand, the potentially harmful effect of high oxygen concentrations in tissues have been less widely discussed (Chen et al., 1995; Tarpy and Celli, 1995; Vincent et al., 2017). Hyperoxia has been shown to be toxic in a variety of animal models; a few published data demonstrate similar effects in humans (Carpagnano et al., 2004; Clark and Lambertsen, 1971; Klein, 1990; Montgomery et al., 1989; Sackner et al., 1975; Vincent et al., 2017). There is increasing evidence that oxidative stress is implicated in the development of airway inflammation and reactive oxygen species might play an important role in the modulation of airway inflammation induced by hyperoxia. Budinger and Sznajder reported that hyperoxic lung injury including damage of membrane receptors, channels, membrane of mitochondria, resulted from the activation of cellular-signaling pathways susceptible to modulation (Budinger and Sznajder, 2005).

This review article summarizes the effect of hyperoxia with a special focus on the respiratory reflexes, namely on the cough reflex. The mechanisms underlying changes in the cough reflex sensitivity are incompletely understood. Because the lungs are directly exposed to high levels of oxygen, there is no doubt that respiratory epithelium is a major target for oxidative injury that manifested in lung function changes including cough. Information about hyperoxia-related cough response is still limited. On the basis of available information we supposed that hyperoxia alone or in combination with primary lung tissue injury should have a damaging effect on lung tissue, including the airway nerve endings with the changes in the sensitivity of the central and peripheral neuronal pathways regulating cough (Kollarik and Undem, 2003; Mazzone and Canning, 2002).

We have previously demonstrated that long-term exposure to 100% oxygen inhibits the cough provoked by mechanical stimulation of large airway mucosa in healthy cats (Hanacek et al., 1996a). Here, we addressed the hypothesis that hyperoxia that suppressed coughing in that model is accompanied by decrease in cough reflex sensitivity. This hypothesis was validated in guinea pig model using different concentrations of oxygen and different time of exposure (Hanacek et al., 1996b, 1998). We have also studied effects of hyperoxia in different models of primary lung tissue injury including allergic airway inflammation or neuropathic damage (Brozmanova et al., 2002, 2004).

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This model is likely relevant for understanding effects developed by long-term oxygen therapy used for treatment of chronic respiratory diseases. We also present information of the potential role of antioxidants in reversal of the detrimental effects of hyperoxia on the cough reflex (Brozmanova et al., 2006, 2007a, 2007b). In this review article we carried out additional analysis of the experiments from previously published and unpublished studies and data obtained in the guinea pig model of hyperoxia were pooled and analysed for the cough reflex sensitivity (Brozmanova et al., 2002, 2004, 2006, 2007a; Brozmanova et al., 2007b; Hanacek et al., 1996a, 1996b; Hanacek et al., 1998).

2. Hyperoxia-induced oxidative stress and putative mechanism of injury

The development of hyperoxic lung injury has been clearly shown to require the generation of reactive oxygen species (ROS) and other related radicals such as reactive nitrogen species (RNS), which lead to alveolar epithelial and endothelial damage through their ability to react with and damage essential biomolecules, including enzymes, membrane lipids, and nucleic acids (Jenkinson, 1993). The most common ROS include superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radicals (OH^-), and singlet oxygen ($^1O_2$) (Klein, 1990; Gille and Sigler, 1995). The nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system, in conjunction with mitochondria, is the major site of ROS generation during hyperoxia and hyperoxia-induced oxidative stress refers to the imbalance caused by increased formation of ROS and/or deficient antioxidants (Gille and Sigler, 1995; Helmerhost et al., 2015; Klein, 1990; Zaher et al., 2007).

Major harmful effects of hyperoxia occur on the molecular level (protein oxidation, lipid peroxidation, damage to DNA) and cellular level (effect on signal transduction, on cell membrane functions and on gene expression). Lipid peroxidation results in disruption of the cell or neural membrane with consequent interruption of cellular signaling. Oxidative protein damage alters the conformation of receptors, enzymes and signal pathways resulting in altered function (Budinger and Sznajder, 2005; Gille and Sigler, 1995; Helmerhost et al., 2015). Oxidative injury by ROS may result in DNA strand breaks, with abnormal replication and transcription. Thus, oxidative stress may produce a wide spectrum of injury, ranging from modulation of gene expression to altered cell growth and necrosis (Budinger and Sznajder, 2005; Helmerhost et al., 2015).

Hyperoxia-induced lung injury can be considered as bimodal process resulting from direct oxygen toxicity and from induced leucocyte infiltration and the accumulation of inflammatory mediators within the lungs (Pagano and Barazzone-Argiroffo, 2003; Zaher et al., 2007). Direct oxygen toxicity is accompanied by the generation of excessive reactive oxygen species leading to alveolar and endothelial damage by destruction of a great variety of important biomolecules including proteins, enzymes, membrane lipids and nucleic acids. In addition, hyperoxic exposure triggers an inflammatory response which exacerbates oxidative toxicity. Secondary pulmonary infection resulting from attenuation of mucociliary transport and alveolar macrophages functions contributes to secondary effect of pulmonary oxygen toxicity. Alongside, both apoptosis and necrosis have been described in alveolar epithelial and endothelial cells during hyperoxia (Pagano and Barazzone-Argiroffo, 2003; Zaher et al., 2007). Hyperoxic lung injury is associated with the activation of a number of transcription factors, including NF-κB (nuclear factor kappa B) and increased expression of different cytokines (i.e. interleukin IL-8) and CXC chemokines, those have been essential mediators of leucocyte infiltration in lung tissues (Zaher et al., 2007). In addition, hyperoxic lung injury includes damage of membrane receptors, channels, membrane of mitochondria, defects in axonal transport, growth factor deficiency, aberrant RNA metabolism (Budinger and Sznajder, 2005), those should be considered the putative mechanisms of toxicity targeting neurons responsible for coughing including oxidative damage.

3. Supplementation of antioxidants against reactive oxygen species

Oxidant-antioxidant homeostasis is highly regulated and essential for maintaining cellular and biochemical functions. Antioxidant defence may be classified as non-enzymatic and enzymatic and can be endogenous and dietary. Accumulation of ROS is usually prevented by cellular enzymes such as superoxide dismutase, catalase, and components of the glutathione redox cycle, including glutathione peroxidase and glutathione reductase. Examples of non-enzymatic antioxidants include glutathione (GSH), ascorbic acid, vitamin E, beta-carotene, and uric acid – all of which reduce ROS to less harmful molecules (Cadenas et al., 1995; Mach et al., 2011).

There is increasing evidence of protective and preventive effects of antioxidant supplementation in different disorders including chronic respiratory diseases. This raises the possibility that combined dietary antioxidant vitamins could affect oxidant-antioxidant imbalance, diminish oxidative damage, and minimize airway inflammation (Cadenas et al., 1995; Pagano and Barazzone-Argiroffo, 2003). There are various options to enhance the lung antioxidant screen. One approach would simply be administration of antioxidant therapy using vitamin C and vitamin E, which reduces oxidative stress in patients with COPD (MacNee, 2000) and other related diseases (Hubbard and Fogarty, 2004). Vitamin E, with the most active compound alpha-tocopherol, is a lipophilic chain-breaking antioxidant; it acts by stopping the chain reaction involved in lipid peroxidation. Vitamin C or L-ascorbic acid is hydrophilic and may quench radicals in the non-lipid cellular compartments (Jacob, 1995). There is considerable evidence of synergistic interaction between these vitamins. Ascorbic acid also protects biomembranes against peroxidation by enhancing the activity of alpha-tocopherol. Ascorbic acid reduces the tocopheroxyl radical and thereby restores the radical scavenging activity of alpha-tocopherol. Thus, it seems a reasonable assumption that concomitant supplementation with vitamin C and vitamin E might enhance pulmonary antioxidant capacity and pulmonary defence against hyperoxia-induced oxygen toxicity. On the other hand, although oxidative stress is implicated in the aetiology of diseases, many supplementation trials with antioxidants have not shown the expected beneficial effects. Some authors have shown no evidence of synergic or cooperative interaction between vitamin C and E on DNA damage or lipid peroxidation in people with oxidative challenge (Huang et al., 2002; Choi et al., 2004).

More recently, animal and human studies on *N*-acetylcysteine (NAC) have shown it to be a powerful antioxidant and a potential therapeutic agent in the treatment of respiratory diseases, cancer, heart disease, heavy metal toxicity, and other diseases characterized by oxidant-antioxidant imbalance. NAC is a thiol compound endowed with antioxidant properties that reduces lung damage produced by oxidant stress in different experimental models and exerts beneficial effects in pulmonary diseases in which oxidant stress appears pathogenetically relevant (Cotgreave, 1997). Historically, NAC has been used as a mucolytic and expectorant agent in chronic respiratory illnesses. NAC is the acetylated precursor of both the amino acid L-cysteine and reduced glutathione (GSH). The biological activity of NAC is attributed to its sulfhydryl group; while its acetyl substituted amino group affords protection against oxidative and metabolic processes (Sjodin et al., 1989). Langley and Kelly also reported that NAC ameliorates hyperoxic lung injury in the pre-term guinea pig by preventing the increase in BALF protein concentration; on the contrary NAC had no effect on lung glutathione (GSH) concentrations (Langley and Kelly, 1993).

Among other non-enzymatic antioxidants – flavonoids have attracted attention of many investigators and good deals of studies on them were reported (Brusselmans et al., 2005; Cao et al., 2005; Prior and Cao, 2000). Flavonoids are a group of naturally occurring phytochemicals abundantly present in fruits and other plants, and beverages such as wine and tea. In the past two decades, flavonoids have gained enormous interest because of their beneficial health effects such as