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Mini review

Alcoholic lung injury: Metabolic, biochemical and immunological aspects☆

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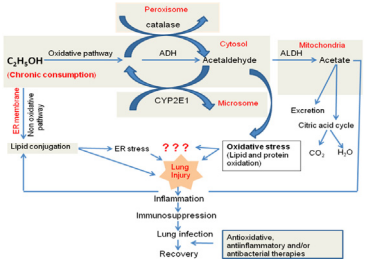
HIGHLIGHTS

- Ethanol-induced immunosuppression and alcoholic lung disease.
- Metabolic basis of alcoholic lung disease.
- Ethanol-induced oxidative stress and endoplasmic stress in lungs.
- Alcoholic lung disease and innate and adaptive immunity.
- Therapeutic approaches for alcoholic lung disease.

GRAPHICAL ABSTRACT



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ABSTRACT

Chronic alcohol abuse is a systemic disorder and a risk factor for acute respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD). A significant amount of ingested alcohol reaches airway passages in the lungs and can be metabolized via oxidative and non-oxidative pathways. About 90% of the ingested alcohol is metabolized via hepatic alcohol dehydrogenase (ADH)-catalyzed oxidative pathway. Alcohol can also be metabolized by cytochrome P450 2E1 (CYP2E1), particularly during chronic alcohol abuse. Both the oxidative pathways, however, are associated with oxidative stress due to the formation of acetaldehyde and/or reactive oxygen species (ROS). Alcohol ingestion is also known to cause endoplasmic reticulum (ER) stress, which can be mediated by oxidative and/or non-oxidative metabolites of ethanol. An acute as well as chronic alcohol ingestions impair protective antioxidants, oxidize reduced glutathione (GSH, cellular antioxidant against ROS and oxidative stress), and suppress innate and adaptive immunity in the lungs. Oxidative stress and suppressed immunity in the lungs of chronic alcohol abusers collectively are considered to be major risk factors for infection and development of pneumonia, and such diseases as ARDS and COPD. Prior human and experimental studies attempted to identify common mechanisms by which alcohol abuse directly causes toxicity to alveolar epithelium and respiratory tract, particularly lungs. In this review, the metabolic basis of lung injury, oxidative and ER stress and immunosuppression in experimental models and alcoholic patients, as well as potential immunomodulatory therapeutic strategies for improving host defenses against alcohol-induced pulmonary infections are discussed.

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Contents

1. Introduction

Chronic alcohol abuse or alcoholism cost ~$223 billion to US economy and 79,000 deaths each year (Bouchery et al., 2011). The worldwide death toll is estimated to be ~30-fold greater than that in the US (CDC, 2004; NIAAA, 2000). Approximately 10–20 million people meet the criteria of alcoholic dependence in the United States and >500 million worldwide (Grant et al., 2004; Lieber, 1995). Alcohol over consumption damages almost every organ in the body and predisposes the host to a wide range of infectious diseases such as pneumonia, acute respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD) (Liang et al., 2012; Pabst et al., 2011; Zhang et al., 2002a). Therefore, chronic alcohol abuse is a major health issue worldwide.

Although ingested alcohol is mainly metabolized in the liver, a sizable amount of the dose reaches the airway passages by the bronchial circulation and is metabolized via oxidative and/or non-oxidative pathways (Manautou et al., 1992; Manautou and Carlson, 1991). Some of this alcohol may be excreted unchanged in exhaled breath. Alcohol consumption compromises systemic immunity, thereby increasing the susceptibility of the host to pulmonary infections characterized by severe symptoms, and less favorable outcomes such as ARDS and COPD (Liang et al., 2012; Moss et al., 1996; Pabst et al., 2011). Both, ARDS and COPD in chronic alcohol abusers result in hospitalization, extensive treatment cost and significant mortalities. Therefore, alcohol abuse is a systemic disorder with specific effects on the respiratory system associated with increased incidence of infections in the lung (Gamble et al., 2006; Shellito, 1998; Vander Top et al., 2005). In this review, we summarize current understanding of ethanol metabolism in the lungs and its consequential oxidative stress and ER stress, suppression of innate and adaptive immunity of the lungs. Finally, we review therapeutic strategies used to mitigate immunosuppression and oxidative stress.

2. Metabolism of alcohol in the lungs

The majority of ingested ethanol is metabolized in the liver by cytosolic alcohol dehydrogenase (ADH) to acetaldehyde, which is further oxidized by mitochondrial aldehyde dehydrogenase (ALDH) to acetate (Lieber, 2004). Mammalian lungs can metabolize ingested ethanol by ADH followed by ALDH at rates dependent on its concentration (Bernstein, 1982; Jones, 1995; Qin and Meng, 2006; Vasiliou and Marselos, 1989; Yin et al., 1992). Ethanol can also be metabolized by microsomal cytochrome P450 2E1 (CYP2E1) and peroxisomal catalase to acetaldehyde in both the liver and in lungs (Bernstein et al., 1990; Jones, 1995; Rikans and Gonzalez, 1990; Yin et al., 1992). CYP2E1 is particularly induced during chronic alcohol abuse and is shown to be responsible for production of reactive oxygen species (Lieber, 2004). However, catalase may not be an important enzyme for ethanol oxidative metabolism due to its inhibition by ethanol (Das and Mukherjee, 2010). Mammalian lung parenchyma consist of large squamous alveolar type I epithelial cells (8% of the cells, but one of the largest cells and cover ~97% of alveolar space area), alveolar type II cells (16% of the total alveolar cells, half that of the type I pneumocyte), capillary endothelial cells (30% of the lung cells) and variable number of alveolar macrophages. Cells in the interstitial space comprised of 37% of the total cells (Matalon, 1991). Whether all cell types in the lungs metabolize ethanol is very poorly studied. Bronchial and bronchiolar epithelium, Clara cells, type II pneumocytes, and alveolar macrophages from human lung have been shown to express CYP enzymes (Hukkanen et al., 2002). Therefore, it is likely that most of resident cells express ethanol oxidizing activity and capable of oxidizing ethanol, but specific information on the metabolism of ethanol in various cell types in the lung is largely lacking.

An alternative metabolism of ethanol is driven by fatty acid ester ethyl ester (FAEE) synthase, phospholipase D, sulfatase and glucuronidase, called as nonoxidative pathway, are also ubiquitous in the mammalian lungs (Aradottir et al., 2006; Lieber, 2004; Manautou and Carlson, 1991; Sharma et al., 1991; Zakhari, 2006). Ethyl sulfate and ethyl glucuronide are water soluble and thus rapidly excreted. On the other hand, phosphatidylethanol (PEt) and FAEEs, the products of nonoxidative metabolism of ethanol catalyzed by phospholipase D and FAEE synthase, respectively, are lipophilic and have been shown to accumulate in target organs including lungs (Aradottir et al., 2002, 2006; Bernstein et al., 1990; Kaphalia et al., 2004; Laposata and Lange, 1986; Manautou and Carlson, 1991). Although toxicity of nonoxidative metabolites of ethanol in mammalian lungs has not been investigated, mammalian lungs are well equipped for both oxidative and non-oxidative metabolism of ethanol and potential target of injury by a wide range of ethanol metabolites formed in the tissue (Fig. 1).

3. Toxicity of ethanol metabolites

Both, ADH- and CYP2E1-catalyzed oxidation of ethanol generate a reactive metabolite acetaldehyde, which readily forms adducts with proteins and causes oxidative stress (Das and Mukherjee, 2010; Jones, 1995; Zakhari, 2006). Oxidative metabolism of ethanol also increases the ratio of NADH to NAD resulting in a dysregulation of lipid metabolism (Day and Yeaman, 1994). Genetic polymorphisms and altered levels of ADH, ALDH and CYP2E1 proteins influence the consumption of and susceptibility to ethanol and is possibly involve organ-specific injuries (Yin, 1994). Once formed, acetaldehyde is rapidly absorbed through the lungs (NIAAA, 2000). Biological consequences of acetaldehyde exposure include reduced phagocytotic index of lung macrophages and degeneration of the nasal olfactory epithelium (Appelman et al., 1986; Wyatt et al., 2012). Malondialdehyde (MDA, lipid peroxidation products) and