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Review

The role of oxidative stress in fetal alcohol spectrum disorders

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ABSTRACT

The ingestion of alcohol/ethanol during pregnancy can result in abnormal fetal development in both humans and a variety of experimental animal models. Depending on the pattern of consumption, the dose, and the period of exposure to ethanol, a myriad of structural and functional deficits can be observed. These teratogenic effects are thought to result from the ethanol-induced dysregulation of a variety of intracellular pathways ultimately culminating in toxicity and cell death. For instance, ethanol exposure can lead to the generation of reactive oxygen species (ROS) and produce an imbalance in the intracellular redox state, leading to an overall increase in oxidative stress. In the present review we will provide an up-to-date summary on the effects of prenatal/neonatal ethanol exposure on the levels of oxidative stress in the central nervous system (CNS) of experimental models of fetal alcohol spectrum disorders (FASD). We will also review the evidence for the use of antioxidants as potential therapeutic strategies for the treatment of some of the neuropathological deficits characteristic of both rodent models of FASD and children afflicted with these disorders. We conclude that an imbalance in the intracellular redox state contributes to the deficits seen in FASD and suggest that antioxidants are potential candidates for the development of novel therapeutic strategies for the treatment of these developmental disorders.

Contents

Abbreviations: ADHD, attention deficit/hyperactivity disorder; ARBD, alcohol-related birth defects; ARND, alcohol-related neurological disorders; ATP, adenosine triphospahe; BAC, blood alcohol concentration; CNS, central nervous system; EtOH, ethanol; FASD, fetal alcohol spectrum disorders; FAS, fetal alcohol syndrome; GD, gestational day; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, reduced glutathione; GSSG, glutathione disulfide; GST, glutathione S-transferase; G6PDH, glucose-6-phosphate-dehydrogenase; H_2O_2, hydrogen peroxide; L-DOPA, levodopa (L-3,4-dihydroxyphenylalanine); MDA, malondialdehyde; NAC, *N*-acetylcysteine; NADPH, reduced nicotinamide adenosine dinucleotide phosphate; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; $NO^{\bullet}$, nitric oxide; NOX, NADPH oxidase; $O_2^{-\bullet}$, superoxide anion radical; $OH^{\bullet}$, hydroxyl radical; PND, postnatal day; ROS, reactive oxygen species; s.c., subcutaneous; SOD, superoxide dismutase; 4HNE, 4-hydroxynonenal; 8-OHdG, 8-hydroxydeoxyguanosine; 8-OxoG, 8-oxoguanine

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1. Introduction

Alcohol is known to be a teratogen and its consumption during pregnancy can produce a wide range of adverse effects in the developing fetus. The severity of fetal damage due to ethanol exposure depends on a number of factors that include the timing, pattern, and dose of ethanol consumed (Abel and Hannigan, 1995; Gil-Mohapel et al., 2010). The term fetal alcohol spectrum disorders (FASD) includes the vast range of pathological conditions that can occur when alcohol is consumed during different periods of the pregnancy (Sokol et al., 2003). The spectrum of disorders can include alcohol-related birth defects (ARBD), alcohol-related neurological disorders (ARND) (Burd and Martsolf, 1989; May et al., 2009; Oesterheld et al., 1998), and fetal alcohol syndrome (FAS). FAS, the most severe condition that results from in utero alcohol exposure, is characterized by a pattern of cranio-facial dysmorphologies (Jones and Smith, 1973; Sokol and Clarren, 1989), growth retardation (Sokol and Clarren, 1989), and central nervous system (CNS) impairment (Jones and Smith, 1973; Sowell et al., 2002). These deficits are generally accompanied by both structural and functional brain damage (Archibald et al., 2001; Autti-Ramo, 2002; Chen et al., 2003; Ikonomidou et al., 2000; Kerns et al., 1997; Klintsova et al., 2007; Roebuck et al., 1998; Streissguth and LaDue, 1987; West et al., 1984).

Prenatal ethanol exposure has been shown to cause an increase in oxidative stress in developing organs, including the brain (Chu et al., 2007; Dembele et al., 2006; Heaton et al., 2002; Heaton et al., 2003b; Petkov et al., 1992; Ramachandran et al., 2001; Reyes et al., 1993; Smith et al., 2005). Indeed, even a brief exposure to ethanol during gestation can produce an imbalance in the brain's intracellular redox state (Dong et al., 2010) that can be correlated with behavioral deficits (Vink et al., 2005), while antioxidants have been repeatedly shown to improve these deficits (Busby et al., 2002; Neese et al., 2004; Reid et al., 1999; Vink et al., 2005) in rodent models of FASD.

In fact, when compared to other organs, the brain is more susceptible to the generation of ROS. It possesses the highest oxygen metabolic rate of any organ in the body as its cells utilize 20% of the oxygen consumed by the entire organism (Sokoloff, 1999), thus having the potential to generate a high quantity of ROS during oxidative phosphorylation. Moreover, brain tissues are rich in unsaturated fatty acids that can be substrates for ROS (Halliwell, 1992; Porter, 1984). Also, some brain regions have a high content of iron (Gerlach et al., 1994), which can further promote the generation of ROS. In addition, several neurotransmitters are autoxidizable (i.e., they can spontaneously react with oxygen). These include dopamine and its precursor levodopa (L-DOPA), serotonin and norepinephrine, and their reaction with oxygen can generate not only superoxide ($O_2^{\bullet-}$), but also quinones and semiquinones that can deplete the levels of the endogenous antioxidant reduced glutathione (GSH) and bind to protein thiol groups, which in turn can be easily oxidized (Spencer et al. 1998).

Given this potential to generate elevated levels of ROS, it is surprising that the antioxidant defense system of the brain is somewhat limited. The activities of the antioxidant enzymes superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) are lower in the brain than in other organs such as the liver or kidney (Floyd and Carney, 1992). In addition, fetal cells are more vulnerable to the neurotoxic effects of oxidative stress than the adult brain since the levels of antioxidant enzymes and of non-enzymatic endogenous antioxidants in the developing fetus are lower when compared to the levels observed in adults (Bergamini et al., 2004; Henderson et al., 1999). For example, brain GPx and glutathione S-transferase (GST) activities at gestational day (GD) 19 are only 41% and 11% of the adult values respectively, while GSH and vitamin E levels are 51% and 20% of the levels found in adulthood (Henderson et al., 1999).

In the present review we will cover the most recent findings in this field and critically analyze their relevance for the understanding of the neuropathology of FASD. Moreover, as there is currently no satisfactory treatment for these disorders, we will also discuss the potential therapeutic value of antioxidants for the mitigation of neuroanatomical and behavioral deficits caused by exposure to alcohol in utero. We believe that the findings reviewed and discussed in this article might also be pertinent to other syndromes that arise as a consequence of prenatal exposure to different substances of abuse and teratogens.

2. Modeling of fetal alcohol spectrum disorder in rodents

Unlike conditions that have well defined pathologies and symptoms, FASD can be influenced by an array of factors ranging from social-economic status to amount, pattern, and timing of alcohol consumption (Ethen et al., 2009; Sokol et al., 2003). Thus the use of animal models is of particular importance in FASD research largely because they impart control over the relatively long list of extraneous variables.