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Review

Effects of pre-natal alcohol exposure on hippocampal synaptic plasticity: Sex, age and methodological considerations

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ABSTRACT

The consumption of alcohol during gestation is detrimental to the developing central nervous system (CNS). The severity of structural and functional brain alterations associated with alcohol intake depends on many factors including the timing and duration of alcohol consumption. The hippocampal formation, a brain region implicated in learning and memory, is highly susceptible to the effects of developmental alcohol exposure. Some of the observed effects of alcohol on learning and memory may be due to changes at the synaptic level, as this teratogen has been repeatedly shown to interfere with hippocampal synaptic plasticity. At the molecular level alcohol interferes with receptor proteins and can disrupt hormones that are important for neuronal signaling and synaptic plasticity. In this review we examine the consequences of prenatal and early postnatal alcohol exposure on hippocampal synaptic plasticity and highlight the numerous factors that can modulate the effects of alcohol. We also discuss some potential mechanisms responsible for these changes as well as emerging therapeutic avenues that are beginning to be explored.

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1. Introduction

Because alcohol readily crosses the placenta, it can cause significant damage to the developing fetus (Guerri and Sanchis, 1985). Currently it is recognized that a variety of disorders can result from prenatal alcohol exposure, and these deficits are assembled under the umbrella-term fetal alcohol spectrum disorder (FASD, Hoyme et al., 2005). Despite efforts from health authorities worldwide informing on the harmful effects of consuming alcohol while pregnant, it has been reported that 13% of women in the United States still consume alcohol during pregnancy (Floyd and Sidhu, 2004). FASD affects 2–5% of the population and is the leading cause of preventable intellectual disabilities (May et al., 2009; Abel and Sokol, 1986).

FASD encompass a myriad of behavioral, cognitive, and anatomical deficits (Patten et al., 2014; Gil-Mohapel et al., 2010; Helfer et al., 2009; Murawski and Stanton, 2011; Thomas et al., 2010) that can persist into adulthood. The most severe disorder that results from pre- and/or early post-natal alcohol exposure (PAE) is Fetal Alcohol Syndrome (FAS). FAS is a disorder characterized by facial dysmorphologies such as midfacial hypoplasia, wide spaced eyes and a smooth philtrum, growth retardation and CNS dysfunction resulting in cognitive, motor, and behavioural problems (Sokol et al., 2003). Since FAS was first defined in the 1970's (Jones and Smith, 1973, 1975) it has been realized that the extent of the damage caused by alcohol can vary due to the timing, frequency and volume of alcohol consumed, as well as the genetics and metabolism of the mother, leading to a wide variability in the severity and symptoms associated with PAE. The disorders that result from PAE are now grouped under the umbrella term FASD, which encompasses children who show various forms of central nervous system (CNS) dysfunction including alcohol-related birth defects (ARBD) and alcohol-related neurological disorders (ARND) that result from PAE but often lack the facial dysmorphology needed to meet the diagnostic criteria for FAS (Sokol et al., 2003; Burd and Martsolf, 1989).

1.1. Effects of alcohol in the central nervous system

Perhaps not surprisingly, the effects of alcohol in the CNS are multi-faceted (Matsumoto, 2009; Santofimia-Castaño et al., 2011). Ironically, one of the reasons that alcohol (or specifically ethanol, CH_3CH_2OH) has such complex actions is due to its simple structure. It has both polar and non-polar attributes making it readily accessible to membranes, receptors and different intracellular structures. For instance, alcohol interacts with membrane bound proteins that include excitatory glutamate and inhibitory γ-aminobutyric acid receptors (GABAR; Ikonomidou, 2000; see Fig. 1). The actions of alcohol on these types of receptors are opposite in that it works as an antagonist on *N*-methyl-D-aspartic acid receptors (NMDARs; Abdollah and Brien, 1995; Hendricson et al., 2004; Mameli et al., 2005; Sanna et al., 1993; Savage et al., 1991) and as an agonist on $GABA_A$ receptors (Proctor et al., 2006; Sanna et al., 2004; Ikonomidou, 2000), thereby affecting synaptic signaling. To further complicate matters, alcohol may even show subunit-specific effects in its ability to alter the function of these receptors (Crews et al., 1996; Grobin et al., 1998). Because receptor subunit expression varies with age and between brain regions, the overall effect of alcohol on synaptic signaling will vary with development and region of interest. Alcohol can also act on voltage-dependent calcium channels whereby presynaptic glutamate release may be attenuated and ultimately affect synaptic transmission (Mameli et al., 2005). In this context it should be mentioned that other neurotransmitters and receptors (see Vengeliene et al., 2008 for a review) also are disturbed by alcohol, however for the purpose of this review, we will mainly focus on the effects of alcohol on the NMDAR and GABAR.

Once inside the cell, alcohol can induce a state of oxidative stress (see Fig. 1; see Section 4.1) by increasing levels of reactive oxygen species that are harmful to the cell (Bondy, 1992; Guerri et al., 1994; Montoliu et al., 2002; Brocardo et al., 2011a). Exposure to alcohol can activate caspase pathways, which may lead to DNA fragmentation and initiation of cell death and neurodegeneration (Olney et al., 2002; Olney, 2004; Pascual et al., 2007; Franke et al., 1997). Within the nucleus, alcohol can interfere with transcription of neurotrophic factors (Miñana et al., 2002; Wilkemeyer, 2002). Furthermore, it can alter cellular metabolism related to synaptic signaling. For instance, chronic alcohol exposure markedly reduces the activity of the astrocyte-specific enzyme glutamine synthetase (Norenberg and Martinez-Hernandez, 1979), which is important for ammonia detoxification and neurotransmitter replenishment (Babu et al., 1994), see Fig. 1).

The primary metabolite of alcohol, acetaldehyde, itself is also teratogenic and can be embryolethal if administered directly to pregnant rats (O'shea and Kaufman, 1979). There has been significant debate in the field regarding whether the observed teratogenic effects associated with PAE are actually due to the alcohol itself or due to the acetaldehyde metabolized from alcohol by alcohol dehydrogenase, as both alcohol and acetaldehyde are readily accessible to the fetus during prenatal development (Blakley and Scott, 1984). When alcohol is delivered (3/3 g/kg, PND 4–9) in conjunction with 4-methylpyrazole, an alcohol dehydrogenase inhibitor, alcohol is prevented from being metabolized into acetaldehyde and produces a BAC that is nearly double to alcohol treatment alone (Chen et al., 1995; Blakley and Scott, 1984). The concurrent treatment of alcohol and 4-methylpyrazole in this study produced greater microencephaly. However, inhibitors of aldehyde dehydrogenase, which normally converts acetaldehyde to acetate, can exacerbate the effects of PAE on the offspring (Jones et al., 1991), however there are studies that show no added effect of disulfiram administration with alcohol in C57BL/6J mice (Webster et al., 1983). The data regarding this controversy have yet to provide concrete answers regarding the relative damage caused by alcohol versus acetaldehyde on the developing nervous system as both are present under conditions of alcohol consumption. The inconsistencies between