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Maternal alcohol binge drinking induces persistent neuroinflammation associated with myelin damage and behavioural dysfunctions in offspring mice

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ABSTRACT

Alcohol binge drinking is on the increase in the young adult population, and consumption during pregnancy can be deleterious for foetal development. Maternal alcohol consumption leads to a wide range of long-lasting morphological and behavioural deficiencies known as foetal alcohol spectrum disorders (FASD), associated with neurodevelopmental disabilities. We sought to test the effects of alcohol on neuroimmune system activation and its potential relation to alcohol-induced neurodevelopmental and persistent neurobehavioural effects in offspring after maternal alcohol binge drinking during the prenatal period or in combination with lactation. Pregnant C57BL/6 female mice underwent a procedure for alcohol binge drinking either during gestation or both the gestation and lactation periods. Adult male offspring were assessed for cognitive functions and motor coordination. Early alcohol exposure induced motor coordination impairments in the rotarod test. Object recognition memory was not affected by maternal alcohol binge drinking, but Y-maze performance was impaired in pre- and early postnatal alcohol-exposed mice. Behavioural effects were associated with an upregulation of pro-inflammatory signalling (Toll-like receptor 4, nuclear factor-*kappa* B p65, NOD-like receptor protein 3, caspase-1, and interleukin-1β), gliosis, neuronal cell death and a reduction in several structural myelin proteins (myelin-associated glycoprotein, myelin basic protein, myelin proteolipid protein and myelin regulatory factor) in both the prefrontal cortex and hippocampus of adult mice exposed to alcohol. Altogether, our results reveal that maternal binge-like alcohol consumption induces neuroinflammation and myelin damage in the brains of offspring and that such effects may underlie the persistent cognitive and behavioural impairments observed in FASD.

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1. Introduction

The developing central nervous system (CNS) is particularly vulnerable to the toxic effects of alcohol (Alfonso-Loeches and Guerri, 2011; Andersen, 2003). Indeed, alcohol exposure *in utero* may lead to a wide range of long-lasting physical, cognitive and neurobehavioural anomalies, collectively known as foetal alcohol spectrum disorders (FASD), in offspring (Dörrie et al., 2014; Jacobson and Jacobson, 2002; Larkby et al., 1997; Sokol et al., 2003), with foetal alcohol syndrome (FAS) as the most severe form of the FASD spectrum, characterized by gross skeletal and craniofacial abnormalities and severe CNS alterations (Jones and

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Abbreviations

AP-1	Activator Protein-1
BAC	Blood Alcohol Concentration
CNS	Central Nervous System
DID	Drinking in the dark
FAS	Foetal Alcohol Syndrome
FASD	Foetal Alcohol Spectrum Disorders
GAPDH	Glyceraldehyde 3-phosphate Dehydrogenase
GC-FID	Gas Chromatography-Flame Ionization Detector
HMGB1	High-mobility Group Box 1
HPC	Hippocampus
IL	Interleukin
LMNA	Lamin A/C
MAG	Myelin-associated Glycoprotein
MBP	Myelin Basic Protein
MIA	Maternal Immune Activation
MYRF	Myelin Regulatory Factor
NF-κB p65	Nuclear Factor-*kappa* B p65 Subunit
NLRP3	NOD-like Receptor Protein 3
PAE	Prenatal Alcohol-exposed
PD	Postnatal Day
PFC	Prefrontal Cortex
PLAE:	Prenatal and Lactation Alcohol-exposed
PLP	Myelin Proteolipid Protein
ROS	Reactive Oxygen Species
TLR	Toll-like Receptor
VLN	Vinculin

Smith, 1973). Despite its preventability, FASD remains a leading cause of neurodevelopmental disability, affecting between 2% and 5% of the population in the United States and western Europe (CDC, 2016; May et al., 2014). Some studies have shown that heavy episodic drinking throughout pregnancy is associated with severe risks of neurodegeneration and cognitive damage (Flak et al., 2014; Saito et al., 2016). However, there are some discrepancies in the literature addressing the neurobiological consequences of alcohol bingeing during critical periods of brain development. Such differences may be due to the developmental timing of alcohol exposure, which markedly influences the neurobehavioural dysfunction outcome as each brain region has its own sensitive developmental period (Alfonso-Loeches and Guerri, 2011; Sadrian et al., 2014). In addition, other biological and environmental factors can influence the extent of alcohol-induced damage in the developing brain, such as the dose and the exposure pattern of alcohol, the mother's and foetus's genetic background, maternal nutrition and synergistic reactions with other drugs.

The molecular mechanisms of alcohol-induced neuroteratogenesis are complex, and different studies have demonstrated that alcohol disrupts the formation of the developing CNS by interfering with several molecular, biochemical and cellular events required for neurodevelopment (Alfonso-Loeches and Guerri, 2011; Guerri et al., 2009; Most et al., 2014), leading to long-term cognitive and behavioural dysfunction. Recent studies have shown that alcohol can activate the innate neuroimmune system, contributing to brain damage and neurodegeneration in adults and adolescents (Crews et al., 2015; Montesinos et al., 2016). These studies demonstrate that alcohol intake stimulates brain immune cells, microglia and astrocytes (Alfonso-Loeches et al., 2010; Fernandez-Lizarbe et al., 2009) by activating innate immune receptors, Toll-like receptors (TLRs) and NOD -like receptors, and by triggering signalling pathways that culminate in the production of pro-inflammatory cytokines and chemokines, leading to neuroinflammation, myelin alterations and neural damage (Alfonso-Loeches et al., 2012, 2010; Crews et al., 2015; Montesinos et al., 2016, 2015). However, although the role of neuroimmune system activation in the pathogenesis of FAS has been scarcely addressed, some recent studies have shown that alcohol exposure during the neonatal period causes microglial activation and the release of cytokines, suggesting an activation of the immune response (Drew and Kane, 2014; Topper et al., 2015). Interestingly, maternal immune activation (MIA) and inflammation during foetal and neonatal life also affect critical phases of brain development and contribute to the development of neurological and mental disorders (see revs. Hagberg et al., 2015, 2012) through a mechanism involving the activation of TLRs (Hagberg et al., 2015).

The present study aims to evaluate the effects of alcohol on neuroimmune-related biomarkers in the offspring of dams exposed to alcohol bingeing during gestation, with and without lactation. To our knowledge, this is the first study to assess the effects of prenatal and lactational binge alcohol exposure using an animal model of voluntary maternal binge-like alcohol consumption as most of the previous studies used *ad libitum* oral access, an inhaler or a parenteral route of alcohol administration at different stages of gestation (Patten et al., 2014). In addition, the molecular alterations induced by foetal and postnatal alcohol exposure were studied, especially those related to the neuroimmune response and its relation to myelination processes and neural damage in specific brain areas, such as the prefrontal cortex (PFC) and hippocampus (HPC) of mice exposed to binge alcohol consumption during early development, potentially contributing to the behavioural outcome.

It should be emphasized that the experimental model used in the present study reproduces a realistic human situation. Furthermore, we extended alcohol exposure to weaning as most mothers who drink during pregnancy continue to do so when breastfeeding, thus transferring alcohol to infants through their milk (Haastrup et al., 2014). The first 10 postnatal days in rodents are approximately equivalent to the third human gestational trimester, thus covering the entire human-equivalent gestational period (Alfonso-Loeches and Guerri, 2011; Patten et al., 2014). To reproduce an episodic pattern of excessive alcohol drinking during pregnancy and lactation periods, we exposed pregnant and nursing C57BL/6 female mice to an alcohol solution using the drinking-in-the-dark (DID) test paradigm (Rhodes et al., 2005), which has been proposed as a useful binge drinking model of FASD (Boehm et al., 2008). Subsequently, male offspring were assessed for their cognitive and motor function at adulthood. Motor coordination was evaluated by means of the rotarod test. Working and recognition memory were assessed using the Y-maze and the object recognition test, respectively.

2. Materials and methods

2.1. Animals

Male and female C57BL/6 inbred mice were purchased from Charles River (Barcelona, Spain) and shipped to our animal facility (UBIOMEX, PRBB) to be used as breeders. Animals were 12 weeks old when breeding began and were individually housed in standard cages in a temperature- (21 ± 1 °C), humidity- (55% ± 10%) and light-cycle-controlled room. Lighting was maintained during a 12-h

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