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Alcohol and pregnancy: Effects on maternal care, HPA axis function, and hippocampal neurogenesis in adult females

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Summary Chronic alcohol consumption negatively affects health, and has additional consequences if consumption occurs during pregnancy as prenatal alcohol exposure adversely affects offspring development. While much is known on the effects of prenatal alcohol exposure in offspring less is known about effects of alcohol in dams. Here, we examine whether chronic alcohol consumption during gestation alters maternal behavior, hippocampal neurogenesis and HPA axis activity in late postpartum female rats compared with nulliparous rats. Rats were assigned to alcohol, pair-fed or *ad libitum* control treatment groups for 21 days (for pregnant rats, this occurred gestation days 1—21). Maternal behavior was assessed throughout the postpartum period. Twenty-one days after alcohol exposure, we assessed doublecortin (DCX) (an endogenous protein expressed in immature neurons) expression in the dorsal and ventral hippocampus and HPA axis activity. Alcohol consumption during pregnancy reduced nursing and increased self-directed and negative behaviors, but spared licking and grooming behavior. Alcohol consumption increased corticosterone and adrenal mass only in nulliparous females. Surprisingly, alcohol consumption did not alter DCX-expressing cell density. However, postpartum females had fewer DCX-expressing cells (and of these cells more immature proliferating cells but fewer postmitotic cells) than nulliparous females. Collectively, these data suggest that alcohol consumption during pregnancy disrupts maternal care without affecting HPA function

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or neurogenesis in dams. Conversely, alcohol altered HPA function in nulliparous females only, suggesting that reproductive experience buffers the long-term effects of alcohol on the HPA axis.

1. Introduction

Clinical and pre-clinical studies have demonstrated that chronic alcohol consumption has negative short- and long-term consequences for physical and mental health. These problems are substantially exacerbated when alcohol consumption occurs during pregnancy, as it can alter the developmental trajectory of the fetus and lead to enduring cognitive, physiological, morphological, neurobiological, and neurobehavioral deficits (Hellemans et al., 2010; Riley et al., 2011; Schneider et al., 2011; Valenzuela et al., 2012; Weinberg et al., 2008). The negative effects of alcohol consumption during pregnancy on offspring development can extend beyond the *in utero* effects, as maternal care may also be altered (O'Connor and Paley, 2006; Pearson et al., 2012). Indeed, the quality of maternal care has long-lasting consequences for the physical and mental health of infants and children (Gershon et al., 2013; Hofer, 1994; Hofer et al., 2008; Kim and Cicchetti, 2006; Murray et al., 1996), findings supported by studies in rodents demonstrating the significant developmental consequences of maternal care (Barha et al., 2007; Champagne et al., 2003; Hellstrom et al., 2012; Lindeyer et al., 2013; Raineki et al., 2012; Weaver et al., 2004). Studies using animal models to investigate the consequences of alcohol consumption during pregnancy on maternal care have reported inconsistent results. Some studies showed that alcohol during pregnancy did not alter maternal behavior (Anandam et al., 1980; Ewart and Cutler, 1979), others showed that pup retrieval was delayed or reduced (Abel, 1978; Ness and Franchina, 1990), and one on the combined exposure to alcohol and nicotine found increased time away from pups (McMurray et al., 2008).

Expression of maternal behavior is the result of the activity of several interconnected brain areas including, the olfactory bulb, medial preoptic area, and amygdala (Olazabal et al., 2013). Although the hippocampus is not a major component of the maternal behavior circuitry, hippocampal lesions can disrupt maternal care — particularly pup retrieval (Kimble et al., 1967; Terlecki and Sainsbury, 1978). Moreover, the hippocampus is extremely vulnerable to long-term alcohol consumption (Beresford et al., 2006) and hippocampal degeneration may contribute to cognitive deficits and depression associated with alcoholism (Crews and Nixon, 2009; Nixon, 2006). Chronic and binge alcohol consumption suppress hippocampal neurogenesis by reducing cell proliferation and cell survival in male and female rodents immediately following exposure (Anderson et al., 2012; Crews et al., 2004; He et al., 2005; Herrera et al., 2003; Nixon and Crews, 2002). However, effects of alcohol may vary if assessed after a period of abstinence. For example, chronic consumption of alcohol (28 days for males, 6 weeks for females), reduced hippocampal neurogenesis after 2 weeks of abstinence in male and female mice (Pang et al., 2013; Stevenson et al., 2009), whereas in male and female rats, voluntary consumption of alcohol for 7 weeks followed by 4 weeks of abstinence increased neurogenesis by increasing cell proliferation (He et al., 2009). Together, these data suggest suppressed neurogenesis may be one component of alcohol-induced neurodegeneration, and increased cell proliferation during abstinence may represent a compensatory response to replace hippocampal neurons once alcohol consumption ceases.

The effects of prenatal alcohol exposure (PAE) on neurogenesis have also been investigated, with data suggesting significant adverse effects of PAE on neurogenesis in both male (Sliwowska et al., 2010) and female (Uban et al., 2010) offspring. However, dynamic effects of alcohol consumption on hippocampal neurogenesis in pregnant females have not been evaluated. Importantly, pregnancy and motherhood alter hippocampal structure and function. For instance, one reproductive experience (primiparity) reduced cell proliferation in the dentate gyrus in the early postpartum period (Darnaudery et al., 2007; Leuner et al., 2007; Pawluski et al., 2009b) and dendritic complexity in the CA3 and CA1 regions shortly after weaning in primiparous females (Pawluski et al., 2009a). In contrast, multiple reproductive experiences increased hippocampal neurogenesis in middle-aged females (Barha et al., 2011; Roes et al., 2014), and it is unknown whether there is a shift from reduced neurogenesis in the late postpartum.

Finally, chronic alcohol consumption can stimulate hypothalamic-pituitary-adrenal (HPA) axis activity in both non-pregnant (Becker, 2012) and pregnant females (Weinberg and Bezio, 1987). Additionally, administration of high concentrations of corticosterone reduced hippocampal neurogenesis in nulliparous (Brummelte and Galea, 2010) and postpartum females (Workman and Galea, unpublished observations). However, it is not known whether the increased HPA activity observed with alcohol intake during pregnancy (Weinberg and Bezio, 1987) persists into the postpartum period, and whether it affects hippocampal neurogenesis after a period of abstinence from alcohol.

Using an animal model of chronic alcohol consumption, we examine how alcohol consumption during pregnancy affects maternal behavior and HPA axis activity. We also assess hippocampal neurogenesis and developmental stage of immature neurons at the end of the postpartum period by staining for doublecortin (DCX), an endogenous protein expressed in immature neurons. As well, we compare the effects of chronic gestational alcohol consumption in postpartum females following their first reproductive experience and nulliparous (reproductively naïve) females to determine whether reproductive experience can buffer the effects of alcohol on neurogenesis and the HPA axis. We hypothesized that: (1) alcohol consumption during gestation will disrupt maternal care even when dams are not exposed to alcohol during the postpartum period; (2) chronic alcohol