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Neonatal alcohol impairs the context preexposure facilitation effect in juvenile rats: Dose-response and post-training consolidation effects

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ABSTRACT

Alcohol exposure on postnatal days (PND) 4-9 in the rat adversely affects hippocampal anatomy and function and impairs performance on a variety of hippocampus-dependent tasks. Exposure during this developmental window reveals a linear relationship between alcohol dose and spatial learning impairment in the context preexposure facilitation effect (CPFE), a hippocampus-dependent variant of contextual fear conditioning. The purpose of the current report was to examine the effect of a range of alcohol doses administered during a narrower window, PND7-9, than previously reported (Experiment 1) and to begin to determine which memory processes involved in this task are impaired by developmental alcohol exposure (Experiment 2). In Experiment 1, rats pups received a single day binge alcohol dose of either 2.75, 4.00, 5.25 g/kg/day or were sham-intubated (SI) from PND7-9. Conditioned freezing during the test day was evident in all dosing groups, except for Group 5.25 g, indicating no graded dose-related behavioral deficits with alcohol exposure limited to PND7-9. In Experiment 2, rat pups were exposed to the highest effective dose from Experiment 1 (5.25 g/kg/day) or were sham intubated over PND7-9. During training, rats remained in the conditioning context for 5-min following immediate shock delivery. During this test of post-shock freezing, both SI and alcohol-exposed rats given prior exposure to the conditioning context showed comparable freezing levels. Since alcohol-exposed rats showed normal post-shock freezing, deficits by these rats on the test day likely reflect a failure to consolidate or retrieve a context-shock association, rather than a deficit in hippocampal conjunctive processes (consolidation, pattern completion) that occur prior to shock on the training day. These findings illustrate the value of the CPFE for characterizing the separable memory processes that are impaired by neonatal alcohol exposure in this task.

Introduction

Fetal alcohol spectrum disorder (FASD) describes a continuum of birth defects caused by maternal intake of alcohol during pregnancy. In humans, developmental alcohol exposure impairs the normal development of many brain regions including the cerebellum and hippocampus (Norman, Crocker, Mattson, & Riley, 2009; Willoughby, Sheard, Nash, & Rovet, 2008). These abnormalities are likely the cause of behavioral deficits in children in a variety of learning and memory tasks, such as eyeblink conditioning and spatial recognition memory (Hamilton, Kodituwakku, Sutherland, & Savage, 2003; Jacobson, Jacobson, Stanton, Meintjes, & Molteno, 2011; Jacobson et al., 2008; Spottiswoode et al., 2011; Uecker & Nadel, 1998). Importantly, the adverse effects of alcohol are largely a result of the timing, pattern and dosage of maternal ethanol consumption (Maier & West, 2001). Rodent model research has been useful in identifying the effects of these variables, especially the effects of different developmental windows of exposure which can't be manipulated and are therefore difficult to study in human FASD. In rat models of FASD, the hippocampus, for example, is particularly vulnerable to damage when alcohol is administered during the neonatal period, which is equivalent to the brain growth spurt during the third-trimester of human pregnancy (Dobbing & Sands, 1979). Binge-like alcohol exposure during this period (PND4-9) produces hippocampal CA1 pyramidal cell loss, following a range of alcohol doses (Livy, Miller, Maier, & West, 2003; Marino, Aksenov, & Kelly, 2004; Murawski, Klintsova, & Stanton, 2012; Tran & Kelly, 2003).

When exposure is limited to PND7-9, CA1 pyramidal cell loss is also evident after administration with a high dose (5.25 g/kg/day; Marino et al., 2004), suggesting hippocampal vulnerability during this narrow time window. At high alcohol doses, neonatal exposure produces behavioral deficits in a variety of hippocampus-dependent learning tasks such as spatial water maze and trace fear conditioning (Goodlett & Johnson, 1997; Hunt, Jacobson, & Torok, 2009). Despite

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high dose exposure, the behavioral deficits seen in these tasks tend to be modest. This may account for the limited data regarding dose-response effects of neonatal alcohol in spatial memory tasks (Murawski & Stanton, 2011). However, previous reports from our laboratory demonstrate that the context preexposure facilitation effect (CPFE) is especially sensitive to neonatal alcohol exposure (Murawski & Stanton, 2010, 2011). The CPFE is a variant of contextual fear conditioning which requires the hippocampus and emphasizes learning of conjunctive representations of context that is incidental rather than reinforcement-driven (Matus-Amat, Higgins, Barrientos, & Rudy, 2004; Rudy, 2009). The CPFE is abolished by alcohol administered during both the PND4-9 and PND7-9 periods of exposure. Additionally, following exposure of either 2.75, 4.00 and 5.25 g/kg/day from PND4-9, the CPFE reveals a linear dose-response curve and a significant negative correlation between test performance and blood alcohol concentration (BAC, Murawski & Stanton, 2011). The current report extends this previous work by examining dose-response effects on CPFE performance when alcohol exposure occurs during a narrower (PND7-9) period of neonatal development. Because the CPFE is particularly sensitive to neonatal alcohol and factors such as the window of exposure greatly determine alcohol effects on the developing brain (Gil-Mohapel, Boehme, Kainer, & Christie, 2010), it is of interest to examine dose-response functions with a more limited window of ethanol exposure by using the CPFE as a comparison with dose-response effects reported with other tasks (Goodlett & Johnson, 1997; Murawski, Jablonski, Brown, & Stanton, 2013).

The CPFE is a 3-day procedure, requiring separable memory processes for each phase (Fig. 1). In the CPFE, preexposure to the context occurs on the first day. This involves encoding the features of the context into a single unified representation (Jablonski, Schiffino, & Stanton, 2012; Rudy, 2009; Rudy & O'Reilly, 1999). Twenty-four hours later, during training, animals given prior exposure to the preexposure/training context use "pattern completion" in which a subset of the contextual features, experienced prior to immediate shock delivery, trigger recall of the entire contextual representation (or "context memory") from the preexposure day, to associate that representation of the context with immediate footshock (Rudy, 2009). Following consolidation of the context-shock association, a test of contextual freezing occurs on the final day (Fanselow, 1990). During the testing session, those rats preexposed to the conditioning context retrieve the context-shock association and freeze more than rats exposed to an alternate context. The latter group shows the "immediate shock deficit," a failure to associate the training context with shock because of insufficient time to encode the context (Fanselow, 1990). In the CPFE, consolidation of the context memory itself can be examined apart from consolidation of the contextual fear memory, since the spatial learning and affective learning processes occur on separate days. This task, then, can be used to determine which memory processes are disrupted by neonatal alcohol exposure. One hypothesis is that alcohol-exposed rats can form conjunctive representations on the preexposure day and context-shock associations on the training day but fail to freeze on the test day because they cannot consolidate the context-shock association after training or cannot retrieve it during testing. This hypothesis can be tested by measuring post-shock freezing on the training day, which indicates that the context-shock association has been encoded at the time of training (Kim, Fanselow, DeCola, & Landeira-Fernandez, 1992; Rudy & Morledge, 1994). We have recently shown that developing rats given prior preexposure to the conditioning context display an increase in post-shock freezing on the training day relative to animals exposed to an alternate context (Jablonski et al., 2012), indicating intact post-shock freezing during the CPFE in developing rats. However, no studies have examined the influence of developmental alcohol exposure on post-shock freezing in the CPFE. The current report extends previous findings (Murawski & Stanton, 2010, 2011), by examining the effects of a range of alcohol doses (2.75, 4.00 and 5.25 g/kg/day) administered from PND7-9 on the CPFE. Experiment 2 extends a test of post-shock freezing to alcohol exposed animals in order to determine which memory processes involved in the CPFE are impaired by developmental alcohol exposure.

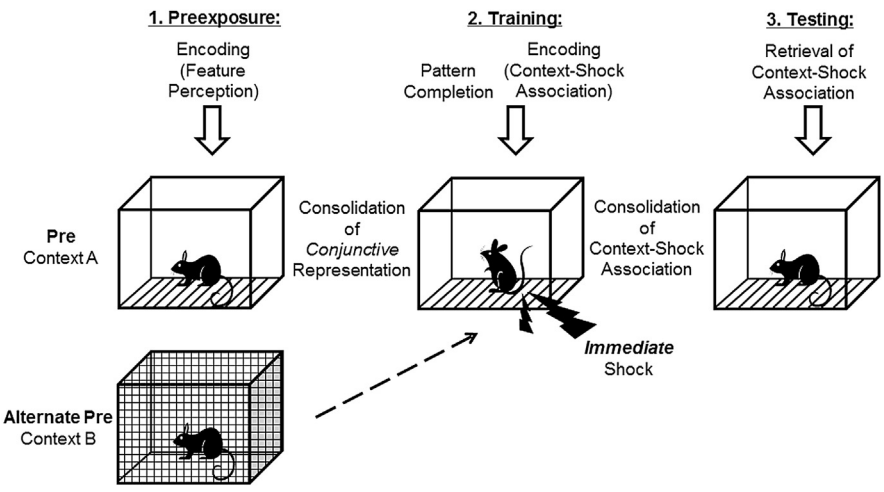

Fig. 1. Schematic diagram of the context preexposure facilitation effect (CPFE) paradigm and associated memory processes. On the first day ('Preexposure') rats are placed in the training context for 5-min (Group Pre) or are exposed to an alternate context (Group Alt-pre). During preexposure, the individual features of the context are bound together in a single-unified conjunctive representation of the context. Following consolidation of the conjunctive representation, 24 h later ('Training'), rats from both preexposure conditions are placed in the training context. Here, pattern completion occurs prior to immediate shock delivery in which a subset of the features are able to elicit retrieval from long-term memory of the entire conjunctive representation in Group Pre but not Group Alt-Pre. Following shock delivery, consolidation of the association of context with shock occurs. After consolidation of the context-shock representation, 24 h later ('Testing'), all rats are returned to the training context at which point freezing behavior (fear to the context) is assessed for 5-min. Because animals preexposed to the training context are able to retrieve the contextual representation memory previously associated with shock, these animals (Group Pre) show an increase in freezing to the context compared to Group Alt-Pre.