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Repeated third trimester-equivalent ethanol exposure inhibits long-term potentiation in the hippocampal CA1 region of neonatal rats

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Abstract

Developmental ethanol exposure damages the hippocampus, causing long-lasting learning and memory deficits. Synaptic plasticity mechanisms (e.g., long-term potentiation [LTP]) contribute to synapse formation and refinement during development. We recently showed that acute ethanol exposure inhibits glutamatergic synaptic transmission and *N*-methyl-D-aspartate receptor (NMDAR)-dependent LTP in the CA1 hippocampal region of postnatal day (P)7–9 rats. The objective of this study was to further characterize the effect of ethanol on LTP in the developing CA1 hippocampus during the third trimester equivalent. To more closely model human ethanol exposure during this period, rat pups were exposed to ethanol vapor (2 or 4.5 g/dL in air, serum ethanol concentrations = 96.6–147.2 or 322–395.6 mg/dL) from P2–9 (4 h/d). Brain slices were prepared immediately after the end of the 4-h exposure on P7–9 and extracellular electrophysiological recordings were performed 1–7 h later under ethanol-free conditions to model early withdrawal. LTP was not different than group-matched controls in the 96.6–147.2 mg/dL group; however, it was impaired in the 322–395.6 mg/dL group. Neither α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor (AMPAR)/NMDAR function nor glutamate release were affected in the 322–395.6 mg/dL ethanol exposure group. These data suggest that repeated in vivo exposure to elevated ethanol doses during the third trimester-equivalent period impairs synaptic plasticity, which may alter maturation of hippocampal circuits and ultimately contribute to the long-lasting cognitive deficits associated with fetal alcohol spectrum disorders. © 2010 Elsevier Inc. All rights reserved.

Keywords: Fetal alcohol syndrome; Development; Plasticity; Glutamate; Synaptic; Neurotransmission

Introduction

Ethanol exposure during fetal development can result in a spectrum of clinical findings (termed fetal alcohol spectrum disorders [FASD]) ranging from relatively mild central nervous system impairments, such as learning and memory deficits, to the most severe manifestation of the disorder—fetal alcohol syndromes (FAS). The clinical hallmarks of FAS include characteristic facial dysmorphology, growth retardation, and impaired central nervous system function. Ethanol has been shown to affect many parts of the brain, including the hippocampus, a region involved in learning and memory (Goodlett and Johnson, 1997; Hamilton et al., 2003; Livy et al., 2003; O'Leary-Moore et al., 2006; Thomas et al., 2002; Thomas et al., 2004; Uecker and Nadel, 1998). Studies with laboratory animals have shown that exposure during the first and second trimester equivalents of human pregnancy can produce long-lasting hippocampal alterations (reviewed in Berman and Hannigan, 2000). In addition, persistent hippocampal dysfunction has been observed in animal models of ethanol exposure during the third trimester equivalent (approximately postnatal day (P)0–12 in rats), and this is illustrated by the results of two behavioral studies that assessed mnemonic performance in rats. Goodlett and Johnson (1997) demonstrated impaired place learning and probe trial search patterns in P26–31 rats, which were exposed to ethanol on P7–9 (blood ethanol concentration ~265 mg/dL). In addition, Thomas et al. (2002) showed that 6 g/kg of ethanol administered on P6 in a binge-like fashion resulted in impaired performance in a spatial discrimination reversal learning task at P40–42. The developmental mechanisms by which ethanol exposure during the third trimester-equivalent produces these long-lasting deficits in hippocampal function are not fully understood.

During the third trimester-equivalent period, intense glutamatergic synapse formation and refinement occur in the hippocampus and these processes are thought to be mediated by long-term potentiation (LTP)-like activity-dependent plasticity mechanisms (Constantine-Paton and Cline, 1998; Durand et al., 1996; Lauri et al., 2007; Leinekugel, 2003; Yasuda et al., 2003; Zhu et al., 2000).

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Experimental evidence suggests that LTP is involved in strengthening of hippocampal synaptic connections, leading to their stabilization during this developmental period (Constantine-Paton and Cline, 1998; Durand et al., 1996; Lauri et al., 2007). We hypothesized that one mechanism by which ethanol could impair hippocampal development is via alterations in synaptic plasticity mechanisms involved in the refinement of neuronal circuitry. This hypothesis is supported by our recent finding that acute ethanol exposure inhibits ionotropic glutamate receptor-mediated responses and LTP induction in the CA1 hippocampal region of P7−9 rat pups (Puglia and Valenzuela, 2010). The objective of this study was to further characterize the effect of ethanol on LTP in the developing CA1 hippocampus during the third trimester equivalent. To more closely model human ethanol exposure during this period, we used an in vivo ethanol vapor exposure paradigm where rat dams and pups were repeatedly exposed to ethanol vapor from P2−9. In this paradigm, blood ethanol concentrations gradually rise and fall, lasting for several hours, as opposed to acute exposure of slices to ethanol where neurons are only briefly exposed to ethanol concentrations that increase and decrease rapidly (Galindo and Valenzuela, 2006). The ethanol vapor exposure paradigm is also advantageous because it minimizes stress in dams and neonates by eliminating the need for maternal separation. Additionally, this paradigm is unlikely to significantly alter maternal care as ethanol levels in the dams are low or undetectable (Galindo and Valenzuela, 2006; Puglia and Valenzuela, 2009). Acute brain slices were prepared from P7−9 rat pups exposed to air or ethanol vapor, and slice electrophysiological techniques were used to investigate LTP and ionotropic glutamate receptor-mediated synaptic transmission.

Experimental procedures

Ethanol vapor chamber exposure paradigm

Animal procedures were approved by the Institutional Animal Care and Use Committee of the University of New Mexico Health Sciences Center and conformed to National Institutes of Health guidelines. Timed-pregnant Sprague−Dawley rats (gestational days 9−17) were obtained from Harlan Laboratories Inc. (Indianapolis, IN). Neonatal rat pups and dams were exposed to 2 or 4.5 g/dL of ethanol vapor, as previously described (Galindo and Valenzuela, 2006; Puglia and Valenzuela, 2009). Briefly, litters were culled to 10 pups on P2, and dams and rat pups were exposed daily for 4 h per day until P9 (Fig. 1A). Exposures were started at 0700 h (lights on at 0600 h and lights off at 1800 h). Ninety-five percent ethanol (Cat #801VWR Tarr, Phoenix, AZ) was vaporized with a heating flask that was regulated with a peristaltic pump. Ethanol vapor mixed with air, or air alone, was delivered to the

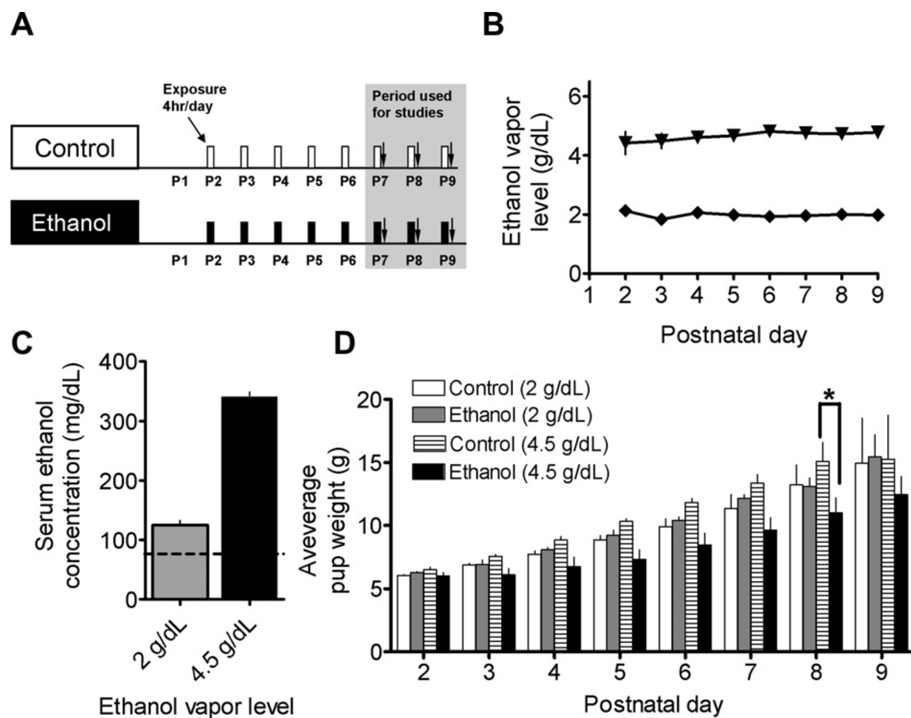

Fig. 1. Third trimester-equivalent ethanol exposure paradigm. (A) Schematic representation of the exposure paradigm where rat pups and their respective dams were repeatedly exposed to ethanol vapor or air (control) for 4 h/d starting on postnatal day (P)2 and continuing to P9. Brain slices for electrophysiology studies were prepared from P7, P8, or P9 rat pups immediately after the 4-h exposure period. (B) Ethanol concentrations in the exposure (vapor) chamber. Note that in most cases error bars are smaller than the symbol. (C) Serum ethanol concentrations were measured from trunk blood samples collected immediately after euthanasia. The dashed line represents the legal intoxication limit (80 mg/dL = 17.4 mM). (D) Average pup weight of control and ethanol vapor-exposed groups as a function of postnatal day. *$P < .05$, by two-way analysis of variance followed by Bonferroni post hoc test.

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