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Research Report

Long-lasting distortion of GABA signaling in MS/DB neurons after binge-like ethanol exposure during initial synaptogenesis

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ABSTRACT

Using a well-established model of binge-like ethanol treatment of rat pups on postnatal days (PD) 4–9, we found that maturation of $GABA_A$ receptor ($GABA_AR$) miniature postsynaptic currents (mPSCs) was substantially blunted for medial septum/diagonal band (MS/DB) neurons in brain slices on PD 11–16. Ethanol reduced mPSC amplitude, frequency, and decay kinetics, while attenuating or exaggerating allosteric actions of zolpidem and allopregnanolone, respectively. The impact of ethanol *in vivo* was long lasting as most changes in MS/DB $GABA_AR$ mPSCs were still observed as late as PD 60–85. Maturing MS/DB neurons in naïve brain slices PD 4–16 showed increasing mPSC frequency, decay kinetics, and zolpidem sensitivity that were nearly identical to our earlier findings in cultured septal neurons (DuBois et al., 2004, 2006). These rapidly developing mPSC parameters continued to mature through the first month of life then stabilized throughout the remainder of the lifespan. Finally, equivalent ethanol-induced alterations in $GABA_AR$ mPSC signaling were present in MS/DB neurons from both male and female animals. Previously, we showed ethanol treatment of cultured embryonic day 20 septal neurons distorts the maturation of $GABA_AR$ mPSCs predicting that early stages of GABAergic transmission in MS/DB neurons are vulnerable to intoxication injury (DuBois et al., 2004, 2006). Since the overall character, timing, and magnitude of GABAergic mPSC developmental- and ethanol-induced changes in the *in vivo* model so closely mirror chronologically equivalent adaptations in cultured septal neurons, this suggests that such parallel models of ethanol impairment of GABAergic synaptic development *in vivo* and *in vitro* should be useful for translational studies exploring the efficacy and mechanism of action of potential therapeutic interventions from the cellular to whole animal level.

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1. Introduction

The medial septum/diagonal band (MS/DB) is a significant component of the limbic system and plays an important role in theta rhythm as well as regulation of hippocampal spatial learning and memory mechanisms through the cholinergic, GABAergic, and glutamatergic projections of the septo-hippocampal pathway (Arjona et al., 2006; Colom et al., 2005; Dwyer et al., 2007; Hindson et al., 1982; Yoder and Pang, 2005). Ethanol is a teratogen that can cause embryonic death, or in those surviving to term, a range of varying phenotypes including retarded growth, various physical malformations, and/or cognitive deficits now collectively recognized as fetal alcohol spectrum disorders (FASD) (Lupton et al., 2004; Riley and McGee, 2005). The wide range in predicted prevalence and degree of injury suggest that many offspring who have had some degree of injurious ethanol exposure in utero likely go unidentified (Riley and McGee, 2005). Injury to developing septo-hippocampal neurocircuits may contribute to deficits in spatial learning and memory found both in children with FASD (Hamilton et al., 2003) as well as in animal models (Goodlett and Johnson, 1997; Mitchell et al., 2000; Savage et al., 1992). How ethanol impairs learning and memory mechanisms requiring the MS/DB and hippocampus is unknown, but in the absence of gross damage to these structures, subtle changes in the timing or strength of

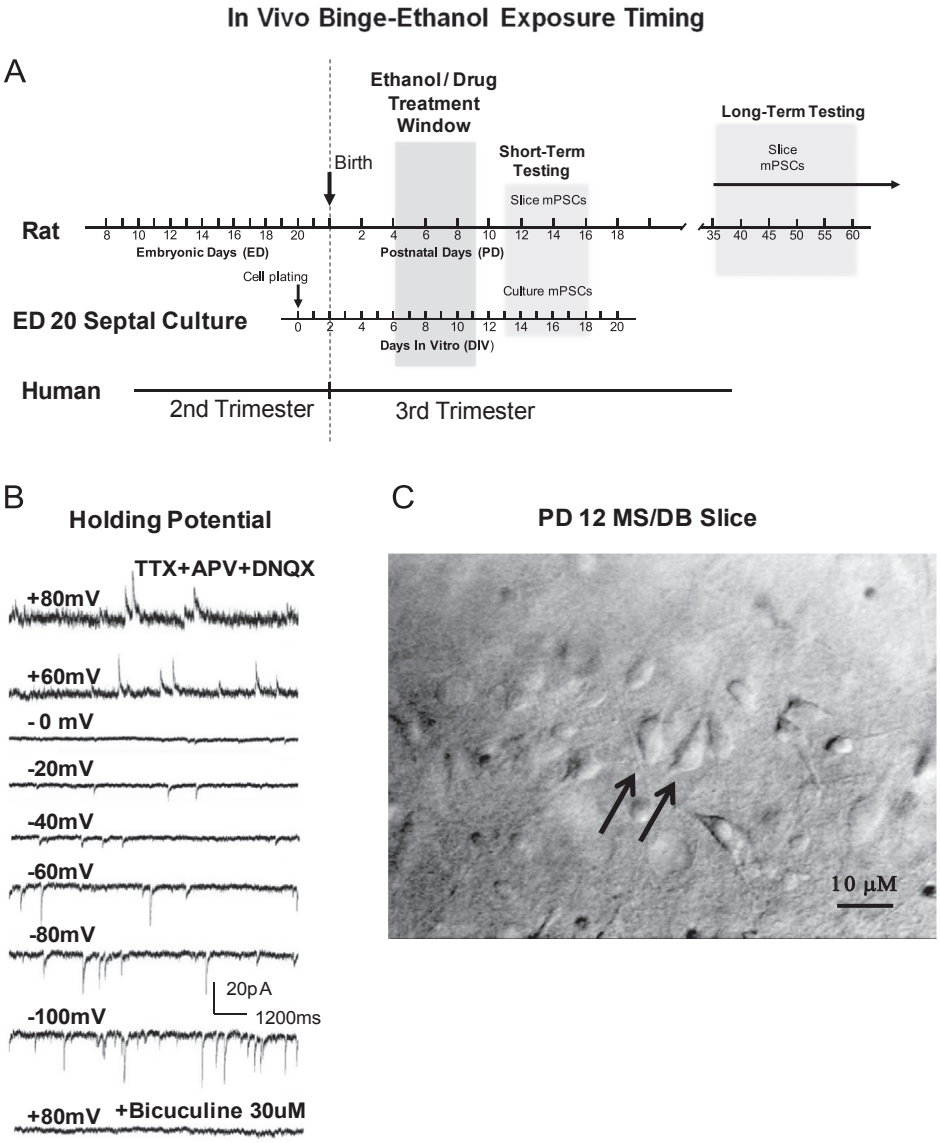

Fig. 1 – Schematic of binge-like ethanol intoxication timing, voltage-dependent whole cell $GABA_AR$ mPSC recordings, and a representative MS/DB rat brain slice. (A) Relative human and rat brain development based on the 'brain growth spurt' concept of Dobbing and Sands (1979). Rats were treated during brain development equivalent to human 3rd trimester and when septo-hippocampal pathway formation is underway. $GABA_AR$ mPSCs were recorded after 'binge ethanol' *in vivo* (ethanol on PD 4–9, then slice recording PD 11–16). (B) $GABA_AR$ mPSCs reverse near 0 mV and are blocked by bicuculline as expected for a $GABA_AR$-mediated chloride conductance under our recording conditions. (C) PD 12 coronal slice showing diagonal band neurons (40 × water immersion, differential interference contrast optics, Olympus BX50WI microscope). Larger, bipolar neurons are indicated by arrows.