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Reduced ethanol drinking following selective cortical interneuron deletion of the GluN2B NMDA receptors subunit

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ABSTRACT

N-Methyl-D-aspartate receptors (NMDAR) are involved in the regulation of alcohol drinking, but the contribution of NMDAR subunits located on specific neuronal populations remains incompletely understood. The current study examined the role of GluN2B-containing NMDARs expressed on cortical principal neurons and cortical interneurons in mouse ethanol drinking. Consumption of escalating concentrations of ethanol was measured in mice with GluN2B gene deletion in either cortical principal neurons ($GluN2B^{CxNULL}$) or interneurons ($GluN2B^{InterNULL}$), using a two-bottle choice paradigm. Results showed that $GluN2B^{InterNULL}$, but not $GluN2B^{CxNULL}$, mice consumed significantly less ethanol, at relatively high concentrations, than non-mutant controls. In a second paradigm in which mice were offered a 15% ethanol concentration, without escalation, $GluN2B^{CxNULL}$ mice were again no different from controls. These findings provide novel evidence for a contribution of interneuronal GluN2B-containing NMDARs in the regulation of ethanol drinking.

Introduction

The transition from moderate to excessive alcohol use is a defining feature of dependence, but the neural mechanisms regulating elevated alcohol (ethanol) drinking remain incompletely understood. One of the primary mechanisms through which ethanol exerts its actions on the brain is disruption of glutamatergic signaling. In particular, ethanol pharmacologically antagonizes the *N*-methyl-D-aspartate receptor (NMDAR) (Lovinger, White, & Weight, 1989; Woodward, 2000) and causes alterations in NMDAR expression and function that have been implicated in the behavioral effects of acute and chronic ethanol exposure, respectively (Bachteler, Economidou, Danysz, Ciccocioppo, & Spanagel, 2005; Holmes, Spanagel, & Krystal, 2013; Nagy, 2004; Radke, Jury, et al., 2015; Seif et al., 2015, 2013; Vengeliene, Bachteler, Danysz, & Spanagel, 2005; Vengeliene, Kiefer, & Spanagel, 2008; Wang et al., 2007, 2010; Wills et al., 2015).

NMDARs are composed of four subunits, only one of which is obligatory (GluN1), and differential expression of the remaining NMDAR subunits alters the receptor's sensitivity to ethanol. NMDARs containing the GluN2B subunit are generally more sensitive to ethanol's antagonist actions (Wills et al., 2012; Woodward, 2000). GluN2B-containing NMDARs are further implicated in the functional effects of chronic ethanol exposure by increased expression of the subunit in cortical, limbic, and striatal regions in rodents repeatedly exposed to ethanol (Follesa & Ticku, 1995; Hardy, Chen, & Wilce, 1999; Kalluri, Mehta, & Ticku, 1998; Kash, Baucum, Conrad, Colbran, & Winder, 2009; Kroener et al., 2012; McGuier, Padula, Mulholland, & Chandler, 2015; Narita, Soma, Mizoguchi, Tseng, & Suzuki, 2000; Nelson, Ur, & Gruol, 2005; Nimitvilai, Lopez, Mulholland, & Woodward, 2015; Pian, Criado, Milner, & Ehlers, 2010; Sheela Rani & Ticku, 2006; Silvestre de Ferron et al., 2015; Wang et al., 2010) and in the hippocampus of human alcoholics (Enoch et al., 2014). There is also evidence that pharmacologically blocking GluN2B (via systemic ifenprodil administration) can reduce ethanol drinking in rats (Vengeliene et al., 2005).

The existing literature suggests that GluN2B is an important target of ethanol and a modulator of ethanol-related behaviors, but does not parse the critical brain regions and neuronal populations where these actions occur. To address this issue in the current study, we determined ethanol-drinking behavior in mutant mice with deletions of GluN2B in specific neuronal populations. Our results reveal a novel role for GluN2B in cortical interneurons but not principal neurons in regulating ethanol drinking.

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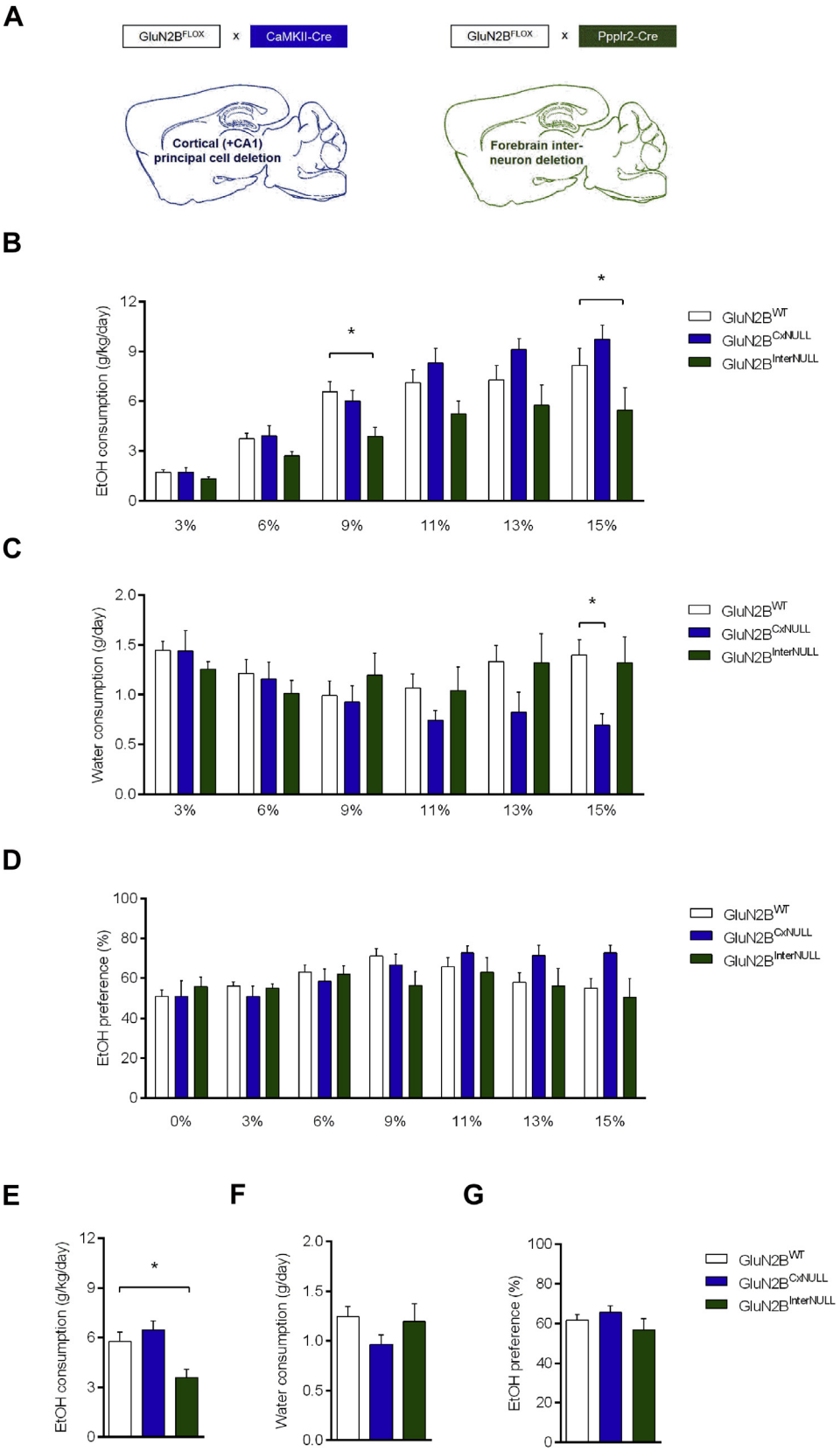

Fig. 1. Effects of GluN2B deletion in specific neuronal populations on ethanol drinking. (A) GluN2B was deleted in cortical principal neurons ($GluN2B^{CxNULL}$; $n = 6$) or cortical interneurons ($GluN2B^{CxNULL}$; $n = 10$). (B) $GluN2B^{InterNULL}$ mice had lower drinking at the 9% and 15% concentrations, as compared to $GluN2B^{WT}$ ($n = 21$) controls. (C) $GluN2B^{CxNULL}$ drank less water than $GluN2B^{WT}$ controls while 15% ethanol was available. (D) Percent preference for ethanol over water did not differ between genotypes. (E) Average ethanol drinking across ethanol concentrations was lower in $GluN2B^{InterNULL}$ mice, relative to $GluN2B^{WT}$ controls. Genotypes did not differ in average water drinking (F) or average percent preference for ethanol over water (G). Data are means ± SEM. $^{*}p < .05$ versus $GluN2B^{WT}$.