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Acute and Chronic Effects of Ethanol on Learning-Related Synaptic Plasticity

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Abstract

Alcoholism is associated with acute and long-term cognitive dysfunction including memory impairment, resulting in substantial disability and cost to society. Thus, understanding how ethanol impairs cognition is essential for developing treatment strategies to dampen its adverse impact. Memory processing is thought to involve persistent, use-dependent changes in synaptic transmission, and ethanol alters the activity of multiple signaling molecules involved in synaptic processing, including modulation of the glutamate and gamma-aminobutyric acid (GABA) transmitter systems that mediate most fast excitatory and inhibitory transmission in the brain. Effects on glutamate and GABA receptors contribute to ethanol-induced changes in long-term potentiation (LTP) and long-term depression (LTD), forms of synaptic plasticity thought to underlie memory acquisition. In this paper, we review the effects of ethanol on learning-related forms of synaptic plasticity with emphasis on changes observed in the hippocampus, a brain region that is critical for encoding contextual and episodic memories. We also include studies in other brain regions as they pertain to altered cognitive and mental function. Comparison of effects in the hippocampus to other brain regions is instructive for understanding the complexities of ethanol's acute and long-term pharmacological consequences.

Keywords

alcohol; long-term potentiation; long-term depression; NMDA receptors; GABA receptors; neurosteroids; acetaldehyde

Introduction

Alcohol intoxication and addiction are major public health problems. In the United States, about 15% of adults have an alcohol-related disorder at some point in their life, and alcohol abuse costs the economy more than $220 billion per year in medical care and lost productivity (Bouchery, Harwood, Sacks, Simon, & Brewer, 2011; Hasin, Stinson, Ogburn, & Grant, 2007). A high percentage of motor vehicle accidents and violent crimes also involve alcohol use, adding to overall societal burden, and alcohol abuse is associated with medical co-morbidities affecting numerous body systems, including the brain and central nervous system (CNS).

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Among the major adverse effects of ethanol is its ability to cause short- and long-term cognitive dysfunction. During milder intoxication (blood alcohol levels [BAL] in the 10–20 mM range), most individuals exhibit motor incoordination and diminished reaction times. With higher BAL (20–40 mM, ~100–200 mg/dL), slowed thinking and altered cognitive processing is observed, and at BAL of 40 mM and above some individuals develop memory "blackouts" (White, 2003). The latter are periods in which individuals perform complex behaviors but have no subsequent recollection. A blackout reflects an acute defect in new memory formation and is a state that can have devastating consequences. In addition to these acute effects, chronic alcohol abuse is associated with persistent impairments in memory and cognition, referred to as "alcoholic dementia" (Oslin & Cary, 2003). Chronic memory problems can also result from nutritional deficiencies associated with ethanol use. Together, these findings strongly support the idea that ethanol is a major risk factor for cognitive dysfunction.

Understanding how ethanol produces its direct effects on memory and cognition is important for developing prevention and treatment strategies to dampen the public health impact of alcoholism. While mechanisms underlying memory are not completely understood, present evidence supports a role for persistent, use-dependent changes in glutamate-mediated excitatory neurotransmission (Martin, Grimwood, & Morris, 2000), with long-term potentiation (LTP) and long-term depression (LTD) being leading candidates as synaptic memory mechanisms (Malenka & Bear, 2004). In this review, we will focus on the effects of ethanol on LTP and LTD. While our emphasis is on acute effects of ethanol, we will also highlight studies that provide insights into longer-term consequences, including studies examining the effects of repeated ethanol intoxication and withdrawal. Because much of the work to date has been done in the hippocampus, a brain region critical for declarative memory formation, we will highlight studies in this region, but we will also describe important results from other brain regions that highlight the complexity of ethanol's CNS actions.

Ethanol and the CNS

Ethanol is an intriguing drug with low molecular weight and solubility in both water and lipid (Deitrich, Dunwiddie, Harris, & Erwin, 1989). The lipid solubility led to early hypotheses that ethanol acts by perturbing cell membranes with secondary effects on cellular proteins. Ethanol thus initially shared a "membrane fluidity hypothesis" with other CNS depressants including general anesthetics (Samson & Harris, 1992). As information about direct effects on proteins evolved and greater information about the molecular structure of proteins became available, emphasis shifted to describing actions on specific signaling systems. It is now clear that ethanol directly alters the activity of numerous ion channels, receptors, and enzymes, and these effects contribute to changes in synaptic function and plasticity (Harris, 1999; Vengeliene, Bilbao, Molander, & Spanagel, 2008).

Among the diverse effects of ethanol, present evidence suggests that changes in glutamatergic and GABAergic neurotransmission, the major fast excitatory and inhibitory transmitter systems in the CNS, determine many of ethanol's acute and long-term properties (Chandler, Harris, & Crews, 1998). There is considerable evidence that ethanol augments the actions of GABA at certain $GABA_A$ receptors ($GABA_ARs$) and inhibits the effects of glutamate at N-methyl-D-aspartate receptors (NMDARs) and kainate receptors (KARs), with additional effects on AMPA type receptors (AMPARs) and metabotropic glutamate receptors (mGluRs). Effects on glutamatergic and GABAergic systems are likely to drive changes in cognition and will be a major focus of this review.

Effects of ethanol on GABA receptors

GABA gates chloride channels (called $GABA_A$Rs) to provide fast inhibitory transmission in the CNS (Sieghart, 1995). $GABA_A$Rs are major sites of action of important sedative, anticonvulsant, and anesthetic drugs including benzodiazepines, barbiturates, neuroactive steroids, and volatile anesthetics. $GABA_A$Rs are pentameric proteins that belong to the cys-loop family of ion channels with 4 membrane-spanning regions per subunit. Multiple $GABA_A$R subunits in several subfamilies (α, β, γ, δ, ε, π, ρ, θ) have been identified, and at least 12 different subunits are expressed in the hippocampus alone, providing substrate for a large array of possible receptor subtypes (Olsen & Sieghart, 2009; Sieghart, 1995). Fortunately, a limited number of subunit combinations appear to dominate brain $GABA_A$R expression, making this a more tractable problem (Olsen & Sieghart, 2008, 2009). Acting at different $GABA_A$Rs, GABA provides two major types of inhibition – fast phasic inhibition associated with release at synapses and slower, more persistent tonic inhibition mediated by extrasynaptic $GABA_A$Rs. Synaptic and extrasynaptic $GABA_A$Rs express different, but sometimes overlapping subunits. For example, synaptic receptors typically contain γ2 subunits, while δ subunits, in the restricted cell populations that express them, are found exclusively in extrasynaptic receptors; γ2 subunits, however, can also be expressed outside of synapses (Farrant & Nusser, 2005; Glykys & Mody, 2007).

Different combinations of subunits markedly influence physiological and pharmacological properties, and ethanol enhances the actions of GABA at some $GABA_A$Rs. Early studies suggested that effects of ethanol are most prominent at receptors expressing γ2L subunits that contain a site for phosphorylation by protein kinase C (PKC) (Wafford et al., 1991), and mice with targeted deletions of the γ isoform of PKC have diminished ethanol sensitivity (Harris et al., 1995). The importance of γ2L has not been observed in all studies and the α1 subunit may be important in determining ethanol effects at some $GABA_A$Rs (Criswell et al., 1993; Mihic, Whiting, & Harris, 1994). Additional subtypes of $GABA_A$Rs may also be highly sensitive to ethanol. These include extrasynaptic receptors expressing α4β3δ and α6β3δ subunits (Criswell & Breese, 2005). In the hippocampus, the α4β3δ subtype (or perhaps α4β2δ) is expressed extrasynaptically in dentate gyrus and contributes to tonic inhibition (Herd et al., 2008; Mody, 2001). This $GABA_A$R was initially reported to be potentiated by ethanol at low mM concentrations (Wallner, Hanchar, & Olsen, 2003), but this result has not been replicated by other groups (Borghese & Harris, 2007; Borghese et al., 2006). Nonetheless, ongoing work has shown the importance of extrasynaptic $GABA_A$Rs, particularly those expressing δ subunits (Meera, Olsen, Otis, & Wallner, 2010). Effects of ethanol on extrasynaptic receptors may also involve modulation by PKCδ (Choi et al., 2008) and changes in receptor surface expression (Suryanarayanan et al., 2011).

Whether effects on $GABA_A$Rs result from direct actions on receptors or from release of endogenous modulators that act alone or in concert with ethanol is uncertain, and may vary by brain region. There is evidence that some ethanol effects are mediated indirectly by increases in GABA-potentiating neurosteroids (Morrow et al., 1999; VanDoren et al., 2000). These neurosteroids include 5α-reduced pregnanes such as allopregnanolone (3α-hydroxy-5αpregnan-20-one, 3α5αP, alloP) and 3α,5α-3,21-dihydroxypregnan-20-one (3α5α-THDOC), agents that are potent and highly effective $GABA_A$R modulators (Belelli & Lambert, 2005; Zorumski, Paul, Izumi, Covey, & Mennerick, 2013). Synthesis of these GABAergic steroids accounts for at least some of ethanol's effects on inhibitory transmission and neuronal firing rates in the CA1 hippocampal region (Roberto et al., 2006; Sanna et al., 2004; Siggins, Roberto, & Nie, 2005; Tokunaga, McDaniel, Morrow, & Matthews, 2003). Furthermore, ethanol and 5α-reduced neuroactive steroids can act synergistically at $GABA_A$Rs to enhance ion channel function (Akk & Steinbach, 2003). Ethanol also promotes the synthesis of neurosteroids locally in the brain, with increases in

steroid levels in the hippocampus within minutes following exposure to 50 mM ethanol (Sanna et al., 2004); both excitatory neurons (Agís-Balboa et al., 2006) and glia (King et al., 2002) contribute to local 5α-reduced steroid synthesis. Presynaptic effects of ethanol also contribute to enhanced inhibition, although this appears to vary across brain regions (Criswell, Ming, Kelm, & Breese, 2008; Roberto et al., 2006; Siggins et al., 2005). At inhibitory synapses onto pyramidal neurons in the hippocampus, the net effect of ethanol is to augment phasic inhibition (Sanna et al., 2004). Interestingly, ethanol may differentially enhance GABAergic synapses onto hippocampal pyramidal neuron cell bodies relative to distal dendritic synapses (Weiner, Gu, & Dunwiddie, 1997). Additionally, both ethanol and neurosteroids may have greater and more potent effects on extrasynaptic $GABA_A$Rs that mediate regional tonic inhibition (Wallner et al., 2003).

Effects of ethanol on glutamate receptors (GluRs)

Glutamate is the brain's major fast excitatory transmitter, and acts at 4 families of receptors. These include ligand-gated ion channels (NMDARs, KARs, and AMPARs) that serve as principal mediators of fast neurotransmission (Dingledine, Borges, Bowie, & Traynelis, 1999; Traynelis et al., 2010), and a group of G-protein-coupled metabotropic receptors (Anwyl, 1999). NMDARs are a site of action of multiple psychoactive drugs including ketamine, phencyclidine (PCP), and nitrous oxide. Native NMDARs typically express GluN1 (NR1) subunits in combination with GluN2 (GluN2A-D, previously called NR2A-D) subunits (Ogden & Traynelis, 2011; Traynelis et al., 2010). At low millimolar concentrations (5–10 mM), similar to levels achieved following 1 or 2 standard drinks (each with ~12 g of alcohol), ethanol non-competitively inhibits NMDARs (Lovinger, White, & Weight, 1989, 1990), affecting ion channel gating rather than agonist binding (Wright, Peoples, & Weight, 1996). Ethanol, however, is a weak NMDAR antagonist and even at very high concentrations (60 mM and above) is only a partial inhibitor. While ethanol is not selective for any particular NMDAR subtype, some evidence suggests preferential inhibition of receptors expressing GluN1/GluN2B subunits (Masood, Wu, Brauneis, & Weight, 1994), a class that is highly sensitive to block by ifenprodil-type agents (Williams, 1993). Other studies indicate that ethanol inhibits receptors containing GluN2A or GluN2B with less effect on those containing GluN2C or GluN2D (Tsai & Coyle, 1998). Ethanol's site of action on NMDARs is not certain, although amino acids in the 3rd and 4th membrane spanning domains in GluN1 and GluN2A are important (Ren, Honse, & Peoples, 2003; Ronald, Mirshahi, & Woodward, 2001). Recent studies in GluN1/GluN2A indicate that 4 pairs of residues in the 3rd and 4th membranespanning domains at the interface between subunits interact with each other to regulate ethanol sensitivity (Ren, Zhao, Dwyer, & Peoples, 2012), with phenylalanine 636 in GluN2A playing a key role (Ren, Zhao, Wu, & Peoples, 2013). This latter residue also influences agonist affinity and channel gating. Evidence does not support actions at sites for other major modulators including Mg^{2+}, glycine, polyamine, and phencyclidine/MK-801 (Chu, Anantharam, & Treistman, 1995). The degree of inhibition, however, may depend on the presence of extracellular Mg^{2+} (Calton, Wilson, & Moore, 1998).

Ethanol also inhibits KARs (Dildy-Mayfield & Harris, 1995; Valenzuela, Bhave, Hoffman, & Harris, 1998). KARs are glutamate-gated channels prominently expressed in hippocampus that participate in transmission at certain synapses. Among other effects, KARs regulate GABA release, and KAR inhibition by low concentrations of ethanol may contribute to ethanol-mediated disinhibition in the CA1 region (Carta, Ariwodola, Weiner, & Valenzuela, 2003). Other evidence suggests that acute and chronic ethanol alters the function of mGluRs linked to phosphoinositide (PI) turnover and mobilization of intracellular Ca^{2+} (Minami, Gereau, Minami, Heinemann, & Harris, 1998; Simonyi, Christian, Sun, & Sun, 2004).

NMDARs and Synaptic Plasticity in the Hippocampus

A potentially important consequence of GluR inhibition is the effect that this has on long-term synaptic plasticity. NMDARs and Group I mGluRs (mGluR1 and mGluR5) play important roles in the induction and modulation of LTP and LTD in the CA1 region (Anwyl, 1999; Hölscher, Gigg, & O'Mara, 1999), an area that is critical for declarative memory formation. LTP refers to a lasting enhancement of transmission that typically follows brief high-frequency activation of glutamate synapses (Bliss & Collingridge, 1993; Malenka & Bear, 2004). Although LTP has been described at glutamate synapses in many brain regions, the process has been most intensively studied in the CA1 Schaffer collateral pathway. Changes underlying LTP last for hours *in vitro* and for days to weeks *in vivo*. These persisting changes make it attractive to view LTP as a synaptic memory mechanism because synapses "remember" that they have experienced certain patterns of activation; that is, these synapses show persistently enhanced responses to an invariant stimulus following particular patterns of activation. Whether an LTP-like process occurs during memory formation *in vivo* is not completely certain. There is evidence that drugs that alter LTP also affect learning (Martin et al., 2000) and experiments using transgenic mice with targeted alterations in key proteins involved in LTP have provided strong correlative, but not universal, support for the hypothesis (Chen & Tonegawa, 1997; Malenka & Bear, 2004; Martin et al., 2000). Work by Bear and colleagues has provided particularly compelling findings in a one-trial inhibitory avoidance-learning paradigm (Whitlock, Heynen, Shuler, & Bear, 2006). Similar considerations exist for LTD, with some evidence suggesting a role for this form of plasticity in novelty processing and one-trial forms of spatial learning (Kemp & Manahan-Vaughan, 2007; Manahan-Vaughan & Braunewell, 1999).

NMDARs play complex roles in synaptic plasticity. Depending on timing and pattern of activation, NMDARs not only promote LTP but also induce homosynaptic LTD or dampen the ability to generate LTP. The latter effect is referred to as "metaplasticity" (modulation of synaptic plasticity) (Abraham & Tate, 1997; Zorumski & Izumi, 2012). When CA1 synapses are activated at 1 Hz for 10–15 min, persisting homosynaptic LTD typically ensues (Dudek & Bear, 1992). Additionally, synapses that have previously undergone LTP can be "depotentiated" by 1 Hz stimulation (Fujii, Saito, Miyakawa, Ito, & Kato, 1991), providing a mechanism for synaptic resetting. The induction of both LTD and LTP-depotentiation (LTP-D), like LTP, is inhibited by NMDAR antagonists and requires Ca^{2+} influx into postsynaptic neurons (Mulkey & Malenka, 1992). Whether synapses exhibit LTP or LTD appears to depend on the degree and timing of increases in postsynaptic Ca^{2+}, and ultimately on the Ca^{2+}-dependent messengers that are activated (Lisman, 1989; Malenka & Bear, 2004). Greater increases in intracellular Ca^{2+} and activation of protein kinases contribute to early phases of LTP whereas activation of protein phosphatases contributes to the initiation of LTD and LTP-D (Mulkey, Endo, Shenolikar, & Malenka, 1994; O'Dell & Kandel, 1994). Specific subtypes of NMDARs may participate in LTP and LTD. Early studies suggested that LTP requires GluN1/GluN2A receptors while LTD requires GluN1/GluN2B (Liu et al., 2004; Massey et al., 2004). More recent studies indicate that LTP involves multiple NMDAR subtypes, including GluN1/GluN2A and GluN1/GluN2B (Berberich et al., 2005; Volianskis et al., 2013). GluN2B-expressing receptors have been more consistently linked to LTD (Brigman et al., 2010), but even here not all studies are consistent (Paoletti, Bellone, & Zhou, 2013). These results suggest that agents with differential effects on NMDAR subtypes may differentially modulate LTP and LTD. Further complicating things, triheteromeric NMDARs with GluN1, GluN2A, and GluN2B subunits are expressed at mature synapses, and this has implications for interpreting the effects of subtype selective antagonists (Paoletti et al., 2013).

Studies outlined above indicate that excitatory synapses, particularly those in area CA1, operate over a range of efficacy and that NMDARs help to determine the effective range. Furthermore, these studies are consistent with the idea that the threshold for synaptic plasticity is dynamic and subject to modulation (Bienenstock, Cooper, & Munro, 1982). In hippocampal slices from young rodents, Dudek and Bear (1992) found that the frequency at which a fixed number of stimuli are delivered to Schaffer collateral inputs determines whether CA1 synapses show LTP, LTD, or no change. When 900 pulses are administered at 1–5 Hz, LTD ensues. The same number of pulses at ~10 Hz produces no lasting change in synaptic efficacy, whereas 900 pulses at 30 Hz or greater produces LTP. This suggests that 10 Hz is a frequency "threshold" for synaptic change. This threshold can be shifted over the course of postnatal development and by specific neuromodulators (Katsuki, Izumi, & Zorumski, 1997).

Acute Effects of Ethanol on Hippocampal Synaptic Plasticity

As noted, an interesting feature of ethanol is its ability to cause acute memory "blackouts" (Nelson et al., 2004; White, 2003). The importance of NMDARs in synaptic plasticity and ethanol's inhibitory actions on these receptors, make it likely that NMDARs mediate at least some of ethanol's effects on memory (Morrisett & Swartzwelder, 1993; White & Swartzwelder, 2004). Although results have been variable, it appears that concentrations of ethanol in the range of 5 to 60 mM inhibit both NMDAR responses and LTP in the CA1 region of hippocampal slices (Table 1) (Chandler et al., 1998). Interestingly, block of NMDARs is only partial at ethanol concentrations that inhibit LTP, and similar partial inhibition of synaptic NMDARs by more selective NMDAR antagonists is insufficient to block LTP (Izumi, Nagashima, Murayama, & Zorumski, 2005c). For reference, a concentration of 50 mM is about 0.2% ethanol (200 mg/dL), a highly intoxicating blood level in most humans (legal intoxication is ~0.08%).

A challenge in interpreting the acute effects of ethanol on LTP is that studies have varied widely in terms of alcohol concentration, age of the animals studied, and recording conditions. Experimental variables (age, ionic conditions, and stimulus parameters) are important because they influence the ease with which LTP can be generated. Table 1 presents an overview of studies examining acute ethanol and LTP in the CA1 region. LTP inhibition typically requires high concentrations of ethanol (in the 40 to 60 mM range), although Blitzer, Gil, & Landau (1990) observed effects at 5 mM in slices from young adult rodents (postnatal day [P] 50–90), and Fujii, Yamazaki, Sugihara, & Wakabayashi (2008) reported dampening at 8.6 mM in adult rats. Pyapali, Turner, Wilson, & Swartzwelder (1999) found that LTP was diminished by 10–30 mM ethanol in slices from P30 (juvenile) rats, but not P90 rats. Other studies report that 18–22 mM ethanol does not block LTP in slices from P30–50 animals (Izumi et al., 2007; Izumi, Nagashima, et al., 2005c; Randall, Lee, Meyer, Wittenberg, & Gruol, 1995). Variables that could contribute to these discrepancies, including brain slice condition, are discussed below and highlighted in Table 1. It is important to consider differences in experimental paradigms because it seems unlikely that low alcohol (< 10 mM) routinely causes profound defects in LTP; otherwise, memory blackouts would be a regular occurrence with only a few standard drinks, something not usually observed. Nonetheless, a dampening of plasticity could contribute to milder dysfunction with low level intoxication, and prior history of alcohol use could modulate these effects through tolerance.

In contrast to LTP, there is much less information about effects of ethanol on hippocampal LTD. Some work suggests that despite inhibitory effects on NMDARs, ethanol may acutely enhance LTD in the CA1 region (Hendricson, Miao, Lippmann, & Morrisett, 2002). As discussed below, this latter observation could involve metaplastic effects of ethanol. It is

also important to consider that LTD, like LTP, is mechanistically complex with several distinct induction mechanisms (Izumi & Zorumski, 2012). These include forms of LTD involving Group I mGluRs, particularly mGluR5. While most studies of ethanol have focused on NMDAR-mediated LTD, Overstreet, Pasternak, Colley, Slater, and Trommer (1997) found that acute ethanol also blocks mGluR-dependent LTD in the hippocampus.

In a series of studies, we examined acute effects of ethanol on NMDAR-dependent LTP and LTD in the CA1 region of P30 rats (Izumi et al., 2007; Izumi, Nagashima, et al., 2005c; Tokuda, Izumi, & Zorumski, 2011). We found that ethanol inhibits both LTP and LTD when administered for 15–30 min prior to and during standard stimuli used to induce LTP and LTD. Effects on LTD mirrored the block of synaptic NMDARs, and ethanol appeared to preferentially inhibit ifenprodil-sensitive (GluN2B-expressing) NMDARs. LTD was significantly diminished by 18 mM ethanol with complete block at 60 mM. Importantly, effects of 60 mM ethanol on LTD, like effects on synaptic NMDARs, were reversible after washout. Effects on LTP were more complex. First, it required ~60 mM ethanol to completely inhibit CA1 LTP during 15–30 min administration, and the effects were slow to reverse (up to several hours) following washout (Fig. 1). Second, LTP block, including the longer-lived inhibition, was overcome by picrotoxin, a $GABA_AR$ antagonist. This suggests that ethanol-mediated effects on inhibitory transmission in addition to, or instead of ethanol-mediated effects on NMDARs contribute to LTP block. These latter results are consistent with other studies showing that effects of ethanol on LTP may not result simply from NMDAR block (Schummers, Bentz, & Browning, 1997; Schummers & Browning, 2001). Recent studies suggest that generation of endogenous GABA-potentiating neurosteroids contributes to effects on LTP (Izumi et al., 2007). Interestingly, 60 mM ethanol also blocked an NMDAR-independent form of LTP that involves L-type voltage-activated calcium channels (Izumi, Nagashima, et al., 2005ca), supporting the idea of more complex effects than NMDAR inhibition alone.

Acute ethanol tolerance and synaptic plasticity

The effects of ethanol outlined above typically result from a rapid increase in ethanol levels to fixed concentrations that are sustained for varying periods (often 15–30 min before and during tetanic stimulation). It is also known that during acute ingestion certain behavioral effects of ethanol diminish despite the presence of high BAL, a phenomenon known as “acute tolerance” (Batista, Prediger, Morato, & Takahashi, 2005; Silveri & Spear, 2004). Acute tolerance may be important in determining susceptibility to alcoholism and its long-term consequences, and has been observed for effects on NMDARs and $GABA_ARs$. Acute tolerance of NMDARs may involve phosphorylation of GluN2B subunits by the tyrosine kinase, Fyn (Miyakawa et al., 1997). During acute exposure, ethanol causes dissociation of the scaffolding protein RACK1 from Fyn, allowing Fyn to phosphorylate GluN2B subunits and enhance function (Yaka, Phamluong, & Ron, 2003). Additionally, acute tolerance of $GABA_ARs$ may reflect changes in receptor phosphorylation (Morrow, VanDoren, Penland, & Matthews, 2001), although changes in presynaptic release of GABA (Ariwodola & Weiner, 2004) and changes in the release of neurosteroids by ethanol (Barbosa & Morato, 2001) may also contribute.

Another factor determining the effects of ethanol involves the rate of rise of ethanol concentration. Clinical manifestations of ethanol intoxication are determined not only by the levels of alcohol achieved but also by the rate of change in ethanol concentration. In most synaptic studies, ethanol is administered at fixed concentrations fairly rapidly and for sustained periods. Thus, relevance to effects observed clinically is uncertain. It is estimated that a single standard drink increases BAL into the low mM range. This makes it unlikely that during a bout of oral intoxication a rise to 50 mM or greater will occur within minutes

even during binge consumption. Tokuda, Zorumski, & Izumi (2007) examined the effects of slower changes in ethanol concentration by increasing ethanol levels in 10 mM increments every 15 min to achieve a final level of 60 mM, a concentration that routinely blocks LTP when administered acutely. Under these circumstances, 60 mM ethanol no longer completely inhibited CA1 LTP. Furthermore, LTP induced under these conditions had unique features, including lack of block by a full NMDAR antagonist, a broad-spectrum mGluR antagonist, or an inhibitor of L-type calcium channels. Interestingly, "ethanol-tolerant LTP" was blocked by inhibiting calcium release from intracellular stores, and the generation of this form of tolerance was prevented by complete NMDAR antagonism during the period of escalating ethanol administration. The latter finding suggests that during ethanol exposure, activation of unblocked NMDARs modulates neuronal function and has consequences for synaptic plasticity.

GABA-enhancing neurosteroids and acute effects of ethanol on LTP

Ethanol can enhance GABA responses in the hippocampus, and changes in inhibitory transmission likely contribute to effects on LTP (Izumi, Nagashima, et al., 2005c; Morrisett & Swartzwelder, 1993; Schummers et al., 1997; Schummers & Browning, 2001). It is not certain which effects of ethanol on GABAergic inhibition contribute to acute LTP block, but there is evidence that ethanol may preferentially augment a form of inhibition in the CA1 region resulting from activation of $GABA_A$Rs near the pyramidal cell body layer (Izumi et al., 2007; Weiner et al., 1997). This proximal inhibition is well positioned to regulate excitability and output of pyramidal neurons and influence synaptic plasticity.

Because other studies found that ethanol promotes synthesis of neurosteroids (Sanna et al., 2004), we examined whether allopregnanolone (alloP), a 5α-reduced neurosteroid that is an effective and potent enhancer of $GABA_A$Rs (Akk et al., 2007; Chisari, Eisenman, Covey, Mennerick, & Zorumski, 2010), altered the effects of ethanol. When administered at levels that had no effect on paired-pulse depression (PPD) of CA1 population spike firing, alloP enhanced PPD in the presence of ethanol (Murayama, Zorumski, & Izumi, 2006). This suggests that GABAergic neurosteroids may contribute to ethanol's ability to modulate local inhibition. Consistent with this, a concentration of alloP that alone had no effect on LTP facilitated ethanol-mediated LTP inhibition (Izumi et al., 2007). In the absence of exogenous alloP, a high acute concentration of ethanol (60 mM) is required to block LTP. In the presence of alloP, significant effects were observed at 20 mM, with complete LTP block at 40 mM. Similarly, Talani, Biggio, & Sanna (2011) found that behavioral stressors associated with increased endogenous neurosteroids (Paul & Purdy, 1992) acutely enhanced sensitivity of LTP to ethanol by a mechanism involving neurosteroid synthesis.

Supporting a role for endogenous neurosteroids in the effects of ethanol on LTP, other studies have found that agents that inhibit alloP synthesis prevent the effects of ethanol on LTP in hippocampal slices (Izumi et al., 2007; Tokuda et al., 2011) (Fig. 1). Similarly, inhibiting the actions of neurosteroids with 17-PA (3α,5α-17-phenyladrost-16-en-ol), a synthetic steroid that blocks the effects of 5α-reduced steroids on $GABA_A$Rs (Mennerick et al., 2004), or removing neurosteroids with a cyclodextrin also overcomes acute LTP inhibition (Izumi et al., 2007). Cyclodextrins are cyclic oligosaccharides that can serve as molecular sponges to scavenge neurosteroids and terminate their actions on $GABA_A$Rs (Shu et al., 2004). Effects of ethanol on proximal inhibition in the CA1 region are also prevented by inhibitors of neurosteroids (Izumi et al., 2007). Taken together, these studies indicate that GABAergic neurosteroids facilitate the effects of ethanol on both local CA1 inhibition and LTP, and that high concentrations of ethanol promote the synthesis of GABAergic neurosteroids contributing to effects on inhibition and LTP. Because neurosteroid levels can be manipulated by a variety of agents and stressors (Tokuda, O'Dell, Izumi, & Zorumski,

2010; Zorumski et al., 2013), these findings have implications for interpreting the concentrations of ethanol that acutely modulate synaptic function. Under conditions in which basal neurosteroid levels are elevated, ethanol is more potent against LTP.

Do metaplastic effects contribute to acute LTP inhibition?

Studies implicating a role for GABAergic steroids in acute ethanol-mediated LTP inhibition strongly suggest that NMDAR block does not account for all effects on LTP. Even at 60 mM, block of synaptic NMDARs by ethanol is only partial (~50% block) and appears to involve ifenprodil-sensitive (GluN2B) NMDARs in the CA1 region of juvenile rats (Izumi, Nagashima, et al., 2005c). This implies that a large fraction of NMDARs remains unblocked, and similar partial inhibition of synaptic NMDARs with ifenprodil or 2-amino-5-phosophovalerate (APV) is insufficient to mimic ethanol's effects on LTP. Furthermore, and differing from effects of ethanol on LTD, LTP inhibition by 60 mM ethanol persists following drug washout (Izumi, Nagashima, et al., 2005c). These observations, coupled with the finding that complete NMDAR block during ethanol administration overcame acute tolerance (Tokuda et al., 2007), led to experiments examining whether complete NMDAR block during ethanol exposure could also overcome effects on LTP. Taking advantage of the prolonged block of LTP following ethanol washout and the fact that APV can be washed out rapidly, Tokuda et al. (2011) found that co-administration of 60 mM ethanol with APV allowed LTP 30 min after both drugs were removed, whereas ethanol alone resulted in persistent LTP inhibition (Fig. 1). Furthermore, the ability of ethanol to stimulate neurosteroid synthesis in CA1 pyramidal neurons was prevented by complete NMDAR block during ethanol administration. Effects of ethanol on neurosteroid immunostaining mirrored the concentration-dependence of LTP inhibition, with no effect at 20 mM but enhanced staining at 60 mM (Tokuda et al., 2011).

Prior studies have shown that low-level tonic NMDAR activation prior to tetanic stimulation can persistently block LTP (Zorumski & Izumi, 2012). This effect is observed with low concentrations of NMDA (e.g., 1 μM × 5 min) that produce no change in basal AMPAR-mediated synaptic transmission (Izumi, Clifford, & Zorumski, 1992a). Persistent LTP block is also achieved by mildly stressful metabolic conditions including low glucose (Izumi & Zorumski, 1997), brief hypoxia (Izumi, Katsuki, Benz, & Zorumski, 1998), and ammonia (Izumi, Izumi, Matsukawa, Funatsu, & Zorumski, 2005a), and following behavioral stress (Kim, Foy, & Thompson, 1996; Yang, Yang, Huang, & Hsu, 2008). In all of these examples, an NMDAR antagonist administered during the stressor paradoxically promotes LTP, implicating untimely, low-level NMDAR activation in LTP inhibition. Interestingly, and of potential relevance to ethanol, antagonists with preference for GluN2A but not GluN2B receptors overcome this LTP inhibition (Izumi, Auberson, & Zorumski, 2006). The effect of the various stressors involves a form of "metaplasticity" and reflects a shift in the relative ease with which LTP can be induced. Furthermore, blocking neurosteroid synthesis with finasteride (or dutasteride) during low NMDA administration (Tokuda et al., 2011) or ammonia (Izumi, Svrakic, O'Dell, & Zorumski, 2013), overcomes LTP inhibition and the ability of these stressors to enhance neurosteroid staining. Metaplastic effects of mild NMDAR activation involve several signaling systems including calcium, calcineurin (and other serine phosphatases), nitric oxide, and p38 MAP kinase (Izumi, Clifford, & Zorumski, 1992b; Izumi, Tokuda, & Zorumski, 2008; Kato, Li, & Zorumski, 1999). Whether ethanol shares this signaling is unknown. Other work has demonstrated a role for tyrosine phosphatases, particularly striatal-enriched protein tyrosine phosphatase (STEP), in ethanol's effects on GluN2B receptors and LTP (Hicklin et al., 2011).

A curious feature of ethanol's acute effects on LTP and neurosteroids is that these actions require high concentrations in naïve hippocampus. As noted, 15–30 min of acute

administration of 20 mM ethanol neither blocks LTP nor promotes neurosteroid synthesis, whereas 60 mM ethanol has both effects (Izumi, Nagashima, et al., 2005c; Tokuda et al., 2011). Coupled with the finding that 20 mM ethanol in the presence of exogenous alloP diminishes LTP (Izumi et al., 2007), we have proposed that ethanol has two effects on LTP – one mediated by lower concentrations (likely involving partial NMDAR antagonism), and the other requiring high ethanol concentrations (Tokuda et al., 2011; Tokuda, Izumi, & Zorumski, 2013a) (Fig. 2). This hypothesis led to studies examining whether a metabolite of ethanol, particularly acetaldehyde, is generated locally in the hippocampus during exposure to high ethanol. Prior studies have suggested that brain-generated acetaldehyde contributes to several effects of ethanol (Correa et al., 2012; Deng & Dietrich, 2008; Quertemont, Tambour, & Tirelli, 2005). Ethanol can be metabolized to acetaldehyde by 3 pathways — alcohol dehydrogenase (ADH), catalase, and cytochrome P450 2E1 (CYP2E1) (Correa et al., 2012; Quertemont et al., 2005). Using inhibitors of these enzymes, we found that ADH, but not catalase or CYP2E1, contributes to effects of 60 mM ethanol on LTP and neurosteroid synthesis in hippocampal slices (Tokuda, Izumi, & Zorumski, 2013a, b). Effects of exogenous acetaldehyde on LTP and neurosteroids were overcome by a full NMDAR antagonist, suggesting that acetaldehyde may trigger ethanol's metaplastic effects. Furthermore, ethanol shows enhanced potency to block LTP in the presence of exogenous acetaldehyde (Tokuda et al., 2013b). The brain expresses several ADH variants (Galter, Carmine, Buervenich, Duester, & Olson, 2003), and hippocampal pyramidal neurons have a variant with low ethanol affinity (Haseba & Ohno, 2010; Mori et al., 2000), consistent with the requirement for high concentrations for effects on LTP and neurosteroids. These findings are also consistent with prior studies demonstrating that acetaldehyde can serve as a trigger for neurosteroid synthesis (Boyd, O'Buckley, & Morrow, 2008), and that an inhibitor of aldehyde dehydrogenase facilitates ethanol's block of LTP in the dentate gyrus *in vivo* (Abe, Yamaguchi, Sugiura, & Saito, 1999).

Chronic effects of ethanol on hippocampal plasticity

Studies outlined above focus on acute effects of ethanol on neuronal function and synaptic plasticity. Because alcoholism is a chronic illness, it is also important to consider longer-term consequences on brain function. It is estimated that over 50% of alcoholics, including detoxified drinkers, exhibit some form of memory problem or cognitive dysfunction (Vetreno, Hall, & Savage, 2011), and alcoholism is recognized as a cause of dementia (Oslin & Cary, 2003). Multiple factors contribute to adverse neuropsychiatric effects of alcoholism, including chronic use, repeated bouts of intoxication and withdrawal, nutritional deficiencies, head injuries, and concurrent medical disorders (Vetreno et al., 2011).

Studies in rodents provide clear evidence that chronic ethanol has adverse effects on synaptic function and synaptic plasticity in the hippocampus and cortex, among other areas (Lovinger & Roberto, 2013; McCool, 2011), and impaired plasticity correlates with defects in learning and memory, particularly spatial learning (Vetreno et al., 2011). Hippocampal slices prepared from rodents treated with ethanol over a prolonged period have diminished ability to generate LTP even when ethanol is withdrawn for one month or more in some studies (Durand & Carlen, 1984; Tremwel & Hunter, 1994). Interestingly, some evidence suggests that a calcium channel blocker overcomes effects of chronic ethanol on LTP (Ripley & Little, 1995), suggesting that intracellular calcium may trigger longer-term consequences.

Important variables in determining the effects of chronic exposure include the dose of ethanol, the pattern of exposure, and drug withdrawal. A chronic intermittent ethanol (CIE) paradigm in rodents has been extremely helpful in exploring long-term binge-like ethanol consumption (Olsen, Liang, Cagetti, & Spigelman, 2005). In this model, there are persistent

changes in both glutamate- and GABA-mediated transmission (Nelson, Ur, & Gruol, 2005). Specific changes include diminished function of $GABA_A$Rs with dampened expression of specific receptor subunits (Cagetti, Liang, Spigelman, & Olsen, 2003). Changes in glutamate transmission include increased expression of GluN2A and GluN2B subunits following withdrawal (Nelson et al., 2005; Qiang, Denny, & Ticku, 2007). These effects are associated with diminished LTP and can recover following ethanol abstinence (Roberto, Nelson, Ur, & Gruol, 2002). The latter changes reflect, in part, altered signaling through the mitogen-activated protein kinase (MAPK) system (Roberto et al., 2003). The CIE model does not result in significant neurodegeneration in the hippocampus or cortex (Nelson et al., 2005). In prefrontal cortex, CIE leads to increased GluN2B expression and altered LTP, possibly contributing to defects in executive function and decision making (Kroener et al., 2012). Adolescent rats exposed to CIE from 30 to 50 days of age exhibit tolerance to ethanol-induced spatial learning defects and exhibit changes in neurosteroid levels in hippocampus and cortex at P50 that reverse by early adulthood (Silvers et al., 2006). Interestingly, a form of ethanol-tolerant, APV-insensitive LTP has been described in rats exposed chronically to ethanol (Fujii et al., 2008), possibly contributing to the behavioral tolerance noted in adolescent animals.

An alternative approach for studying longer-term consequences of alcohol involves continuous exposure models in which animals receive daily ethanol at varying doses over weeks to months (Savage, Candon, & Hohmann, 2000). Unlike CIE, chronically treated rodents show morphological changes and neuronal loss in hippocampus and cortex (Farr, Scherrer, Banks, Flood, & Morley, 2005; Mandyam, 2013; Walker, Barnes, Zornetzer, Hunter, & Kubanis, 1980). Chronic ethanol treatment diminishes LTP in the hippocampus and, again, this correlates with deficits in spatial learning (Hu, Walker, Vickroy, & Peris, 1999; Peris et al., 1997). Effects on LTD have received less attention, but chronic exposure appears to dampen this form of plasticity as well (Thinschmidt, Walker, & King, 2003). Effects on synaptic plasticity are associated with changes in several neurotransmitter systems including changes in GABAergic inhibition as well as diminished acetylcholine signaling and alterations in neurotrophins, particularly brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) (Vetreno et al., 2011). There are also compensatory increases in synaptic NMDARs without effects on extrasynaptic NMDARs (Carpenter-Hyland, Woodward, & Chandler, 2004). Models using chronic ethanol exposure also demonstrate changes in small and large conductance calcium-activated potassium (K^+) channels that contribute to longer-term ethanol tolerance and adaptive plasticity. These latter changes include disrupted interactions between small conductance calcium-activated K^+ (SK) channels and NMDARs (Mulholland et al., 2009).

Ethanol and synaptic plasticity in the amygdala

Lateral/basolateral amygdala

Ethanol has prominent effects on mood and anxiety (McCool, Christian, Diaz, & Läck, 2010). Thus, there is considerable interest in understanding how ethanol modulates function in the amygdala, a brain region intimately involved in networks underlying emotional processing (Johansen, Cain, Ostroff, & LeDoux, 2011). In rodents, long-term forms of synaptic plasticity in the amygdala play key roles in classical fear conditioning, one of the best understood paradigms for emotional learning (Ehrlich et al., 2009). Furthermore, the amygdala has strong connections with the hippocampus where synaptic interactions contribute to contextual aspects of fear learning. The amygdala also has extensive connectivity with other subcortical structures including the bed nucleus of the stria terminalis (BNST) and the striatum. These connections help to regulate anxiety, habits, and motivation. Connections from prefrontal cortex are involved in top-down control over emotions (Johansen et al., 2011).

The amygdala is a group of nuclei that play different roles in emotion (Ehrlich et al., 2009; Johansen et al., 2011). The basolateral amygdala (BLA), particularly the lateral (LA) nucleus, is a major input station that processes information from primary sensory systems in thalamus and cortex, and sends excitatory projections to the central nucleus and BNST. In the LA, LTP of AMPAR-mediated synaptic transmission is associated with fear conditioning, resulting in enhanced behavioral responses to previously innocuous stimuli (Johansen et al., 2011). LA LTP, like CA1 LTP, involves a form of Hebbian plasticity triggered by NMDARs and results in increased expression of synaptic AMPARs and enhanced efficacy of excitatory transmission (Johansen et al., 2011; McCool, 2011). LA LTP is modulated by monoamines, GABA, and glutamate acting at mGluRs, particularly mGluR5 (Ehrlich et al., 2009; McCool, 2011; Roberto, Gilpin, & Siggins, 2012). Ethanol, both acutely and chronically, dampens LA LTP. Acute LTP inhibition involves NMDAR antagonism, although enhanced GABAergic inhibition also likely contributes (Roberto et al., 2012). Chronic ethanol exposure upregulates NMDARs and is associated with enhanced AMPAR synaptic responses (Christian, Alexander, Diaz, Robinson, & McCool, 2012). McCool (2011) has argued that these effects of ethanol usurp mechanisms involved in BLA LTP and reflect a form of ethanol-mediated plasticity that occludes standard LTP. Such effects could account for the ability of ethanol to dampen acute fear conditioning while also resulting in emotional dysregulation during chronic exposure and withdrawal. Importantly, the ability of chronic ethanol and withdrawal to enhance basal AMPAR transmission appears to differ from effects observed in the hippocampus, and mechanisms underlying these changes are not yet certain.

Central amygdala

The central amygdala (CEA) nucleus is another key region in emotional processing. The CEA gets strong excitatory input from BLA and provides the major output of the amygdala, sending GABAergic projections to brain regions involved in emotional expression, including hypothalamus and brainstem (Ehrlich et al., 2009). CEA neurons express receptors for multiple neuromodulators involved in the effects of ethanol, including receiving input from the hypothalamus via CRF (Roberto et al., 2012). Ethanol acutely enhances GABA transmission in the CEA and chronic administration dampens AMPAR- and NMDAR-mediated excitatory responses. Effects of ethanol on NMDARs in CEA may preferentially involve receptors expressing GluN2B subunits (Roberto et al., 2004). Chronic ethanol upregulates GluN2B expression in CEA but not BLA (Roberto et al., 2012), and ethanol withdrawal is associated with enhanced NMDAR responses. Interestingly, chronic ethanol results in enhanced ethanol sensitivity of synaptic NMDARs in CEA, an effect also not observed in BLA. Long-term forms of synaptic plasticity have been described in CEA, including a form of LTP that involves presynaptic NMDARs (Samson & Paré, 2005). Little information is presently available about acute and chronic effects of ethanol on CEA plasticity.

Bed nucleus of the stria terminalis

The amygdala is part of an extended network that includes the striatum and BNST. Like the amygdala, the BNST has subnuclei that play important roles in emotion, including the expression of anxiety (rather than fear). Importantly, the BNST is positioned between amygdala and stress circuitry in the hypothalamic-pituitary-adrenal (HPA) axis and helps to regulate stress responses, including those associated with alcohol intoxication and withdrawal. The BNST is sensitive to modulation by acute and chronic ethanol and plays a role in the behavioral effects of intoxication and withdrawal (Wills & Winder, 2013). As in other regions, glutamate acting at AMPARs and NMDARs plays a key role in synaptic function and plasticity. In multiple subregions of the BNST, ethanol is an effective inhibitor of NMDARs, particularly altering the function of NMDARs containing GluN2B subunits

(Wills et al., 2012). NMDAR inhibition dampens LTP as it does in other brain regions. Similarly, chronic ethanol exposure and withdrawal upregulate NMDAR responses in the BNST (Kash, Baucum, Conrad, Colbran, & Winder, 2009), and this is accompanied by increased expression of GluN2B subunits, a recurring theme seen in other brain regions. Recent work has also shown that the excitability of BNST neurons is dampened in animals withdrawn from chronic ethanol, altering the ability of this region to modulate CeA (Szücs, Berton, Sanna, & Francesconi, 2012).

Effects of ethanol on long-term plasticity in the striatum

Dorsal striatum

The dorsal striatum is the major input to the basal ganglia and regulates initiation and timing of movements, including skilled motor behaviors. This region also plays a key role in instrumental learning and habit formation (Lovinger, 2010). The principal output cells of the striatum are GABAergic medium spiny neurons (MSNs) whose firing is under control of glutamatergic inputs from other brain regions, particularly cortex. Synaptic plasticity in the dorsal striatum has unique features compared to hippocampus, cortex, and amygdala, and this plasticity helps to regulate MSN activity, and motor and habit learning. Although early studies had difficulty demonstrating LTP in the dorsal striatum, it is now clear that cortical glutamatergic inputs onto MSNs exhibit both LTP and LTD (Lovinger, 2010). As is true in many regions, LTP involves NMDARs (Calabresi, Pisani, Mercuri, & Bernardi, 1992), but these receptors are supplemented by D1 and D2 dopamine receptors (D1Rs and D2Rs) and adenosine type 2A receptors (A2ARs) in the direct and indirect pathways (Calabresi et al., 2000; Lovinger, Partridge, & Tang, 2003; Shen, Flajolet, Greengard, & Surmeier, 2008). The direct and indirect pathways refer to different components of the striatum based on inputs and projections. MSNs in the direct pathway project (directly) to substantia nigra pars reticulata and express D1Rs but not D2Rs. In contrast, indirect pathway MSNs express D2Rs and A2ARs, but not D1Rs, and project to the internal segment of the globus pallidus (Grueter, Rothwell, & Malenka, 2012). The cellular and synaptic signaling that drives LTP in both direct and indirect dorsal striatal pathways increases intracellular calcium and activates CamKII, as in other brain regions, with contributions from cyclic AMP via modulatory receptors. The end result, as in other regions, is increased expression of AMPARs at postsynaptic sites on MSNs. Interpreting the roles of specific receptors in LTP is complicated by the fact that the dorsal striatum is not a homogeneous structure, and dorsomedial and dorsolateral aspects of the structure differ in their involvement in skill learning and instrumental conditioning, and use different modulating transmitters to effect synaptic changes. The dorsomedial striatum participates in early skill learning using LTP that involves NMDARs and D1Rs, while the dorsolateral striatum contributes to later phases of this learning and is modulated by CB1 cannabinoid receptors (CB1Rs) and D2Rs. Similarly, the dorsomedial striatum contributes to early phases of instrumental learning using NMDARs and D1Rs, while the dorsolateral region contributes to late phases, perhaps via LTD and the involvement of A2ARs, CB1Rs, and D2Rs (Lovinger, 2010).

LTD in the dorsal striatum also has interesting features. Here LTD induction involves Group I mGluRs (likely both mGluR1 and mGluR5) as well as postsynaptic depolarization. Whereas glutamate release and postsynaptic depolarization typically trigger NMDAR activation in most brain regions, in dorsal striatum, postsynaptic depolarization drives the opening of Cav 1.3 (L-type) voltage-activated calcium channels (VACCs) (Adermark & Lovinger, 2007). The combination of calcium influx via Cav 1.3, calcium release from intracellular stores, and activation of calcium-dependent second messengers results in synthesis and release of an endocannabinoid (EC) (Adermark, Talani, & Lovinger, 2009; Kreitzer & Malenka, 2005). The EC then traverses glutamate synapses in a retrograde fashion to activate presynaptic CB1Rs. At presynaptic terminals, CB1Rs dampen release of

glutamate and produce a persistent decrease in glutamate-mediated transmission. The latter effect may involve altered presynaptic calcium channel function and/or changes in the trafficking of synaptic vesicles. Dopamine plays important roles in LTD in both the indirect and direct dorsal striatal pathways. In the indirect pathway, activation of D2Rs helps to promote LTD (Kreitzer & Malenka, 2005, 2007, 2008), while LTD in the direct pathway requires block of D1Rs (Lüscher & Huber, 2010; Shen et al., 2008). Further complicating LTD in the dorsal striatum, this plasticity is modulated by D2Rs on cholinergic interneurons and a dampening of muscarinic (M1) receptor activation (Wang et al., 2006). Similar to other brain regions, acute ethanol dampens LTP in dorsal striatum in a concentration-dependent fashion. Interestingly, block of LTP can convert LTP into LTD depending on the ethanol concentration and how ethanol is administered (Yin, Park, Adermark, & Lovinger, 2007). A low concentration of ethanol (2 mM) diminishes the magnitude of LTP and 10 mM blocks LTP completely. Thus, dorsal striatal LTP appears to be exquisitely sensitive to modulation by ethanol compared to hippocampus. Furthermore, at 50 mM ethanol, a stimulus that usually results in LTP now produces robust LTD. The timing of ethanol exposure also appears to be important. When 50 mM ethanol is washed out immediately following tetanic stimulation, LTP is blocked and no LTD is observed. When ethanol is washed out 10 min after stimulation, LTD ensues. The mechanisms contributing to these effects are complex because 50 mM ethanol only inhibits synaptic NMDARs by about 25% at striatal synapses, and ethanol-promoted LTD involves both CB1Rs and D2Rs. These results are consistent with other work showing that acute ethanol does not block striatal LTD (Clarke & Adermark, 2010; see also McCool, 2011). Other studies have found that acute effects of ethanol on striatal LTP involve a dampening of second messenger pathways, including ERK, a MAP kinase (Xie et al., 2009). Interestingly, longer-term ethanol dampens striatal LTD, and this effect is associated with altered ERK activity (Cui et al., 2011). Recent data demonstrate that chronic intermittent ethanol also downregulates CB1R signaling and eliminates CB1R-dependent LTD in dorsal striatum, while priming the striatum to play an enhanced role in learning (Depoy et al., 2013). Repeated cycles of ethanol exposure and withdrawal upregulate GluN2B expression and are associated with facilitated LTP that can be blocked by antagonists of GluN2B-expressing NMDARs (Wang et al., 2012; Xia et al., 2006).

Ventral striatum/nucleus accumbens

Like dorsal striatum, the ventral striatum/nucleus accumbens integrates information from multiple brain regions to regulate motor output. Here neural processing plays a key role in motivated behaviors and in the expression of reward signals (Stuber, Hopf, Tye, Chen, & Bonci, 2010). The ventral striatum has high connectivity to limbic and neocortical regions involved in emotion and, in turn, influences plasticity and learning in those other regions. The ventral striatum receives glutamatergic inputs from multiple cortical and subcortical areas, including hippocampus and amygdala, as well as strong innervation from dopamine neurons in the ventral tegmental area (VTA). The various inputs regulate the principal projection neurons in the region, which, like dorsal striatum, are GABAergic MSNs. The nucleus accumbens consists of two major regions – a core region involved in sensorimotor function, reward, and motivation, and a shell area involved in emotion and motor processing. Like dorsal striatum, the ventral striatum has direct and indirect paths, with indirect MSNs expressing higher levels of NMDARs than direct pathway MSNs (Grueter et al., 2012). Virtually all drugs of abuse, including alcohol, modulate activity in the ventral striatum and there is considerable interest in understanding how neuroadaptations in this region contribute to substance abuse and dependence, particularly the propensity to long-term use. Altered plasticity and function in the ventral striatum and the associated VTA contribute strongly to the concept of alcoholism (and drug abuse) as states of aberrant learning (Stuber et al., 2010). Importantly, acute administration of a variety of abused drugs,

including ethanol, enhances dopamine accumulation in the ventral striatum, and this is thought to contribute to rewarding effects of these agents (Koob & Volkow, 2010).

Both direct and indirect pathways in the nucleus accumbens exhibit NMDAR-dependent LTD (Grueter et al., 2012). Stimulation of inputs to the nucleus accumbens from prelimbic cortex also drives mGluR-dependent LTD (Robbe, Kopf, Remaury, Bockaert, & Manzoni, 2002) that involves mGluR 2/3 and changes in the activity of P/Q calcium channels involved in regulating neurotransmitter release (Robbe, Alonso, Chaumont, Bockaert, & Manzoni, 2002). In the core region of the accumbens, indirect pathway MSNs exhibit two forms of mGluR5-dependent LTD (Grueter et al., 2012), a form involving endocannabinoids and another involving activation of postsynaptic transient receptor potential vanilloid type 1 channels (TRPV1). The latter form of LTD has both presynaptic and postsynaptic components (Grueter, Brasnjo, & Malenka, 2010).

In the shell region of the nucleus accumbens, ethanol acutely inhibits NMDAR-dependent LTD in a concentration-dependent fashion with complete block at 40 mM. Interestingly, lower (20 mM) and higher (60 mM) concentrations inhibit LTD to a lesser extent but to the same degree (Jeanes, Buske, & Morrisett, 2011), suggesting a U-type relationship. LTD block is mimicked by NMDAR antagonists with selectivity for GluN2B type receptors. Further complicating things, effects of ethanol on LTD are occluded by a D1R antagonist. Interestingly, exposure to chronic intermittent ethanol (CIE) followed by 24 h of withdrawal resulted in a loss of LTD and conversion to NMDAR-dependent LTP. By 72 h after withdrawal from a 3-day bout of CIE, however, both LTD and LTP are absent (Jeanes et al., 2011).

Other studies in an acute slice preparation indicate that 50 mM ethanol inhibits LTP in the nucleus accumbens via effects on group I mGluRs (mGluR1 and 5) and dampens dopamine release (Mishra, Zhang, & Chergui, 2012). Chronic ethanol also dampens NMDAR function in the nucleus accumbens and depresses NMDAR-dependent LTP. These latter effects correlate with locomotor sensitization to ethanol and enhanced ethanol consumption (Abrahao et al., 2013). Withdrawal from chronic ethanol increases the expression of GluN1 and GluN2B subunits in the nucleus accumbens, along with increased mGluR1. Thus, altered expression of NMDAR subunits (particularly GluN2B) following withdrawal from chronic ethanol appears to be a common theme across multiple brain regions involved in learning, emotion, and motivation.

Ventral tegmental area

The VTA plays a major role in motivation and reward, and, together with the nucleus accumbens, is a key part of the mesolimbic dopamine system (Stuber et al., 2010). The VTA provides major dopaminergic innervation to the ventral striatum and modulates MSN function and synaptic plasticity. This dopamine input is thought to provide critical signals underlying motivation and reward (Kelley, 2004; Wise, 2004). Using a measure of synaptic efficacy based on changes in the ratio of AMPAR to NMDAR synaptic currents, Saal, Dong, Bonci, & Malenka (2003) found that a single *in vivo* exposure to ethanol (20 mg/kg) was sufficient to enhance AMPAR-mediated glutamatergic transmission in midbrain dopamine neurons for at least 24 h (reminiscent of LTP). This use of changes in the AMPAR/NMDAR ratio as an index of synaptic plasticity is based on the trafficking of AMPARs into and out of synapses during LTP and LTD, respectively, and followed earlier work showing that acute cocaine induced a form of LTP (increased AMPAR/NMDAR ratio) at excitatory synapses in the VTA (Ungless, Whistler, Malenka, & Bonci, 2001), while chronic cocaine induced LTD at prefrontal cortical synapses in the nucleus accumbens (Thomas, Beurrier, Bonci, & Malenka, 2001). The augmented responses observed by Saal et al. (2003) were mimicked by acute *in vivo* exposures to other addictive drugs including cocaine, morphine, and nicotine,

and acute behavioral stress, but were not mimicked by fluoxetine (an antidepressant) or carbamazepine (an anticonvulsant). Interestingly, changes in VTA neurons may involve only a specific subtype of neurons that also show increases in dendritic spine density (Sarti, Borgland, Kharazia, & Bonci, 2007). Thus, acute plastic and persisting changes in VTA function may help to determine the addictive potential of certain drugs and to regulate stress-related behavior and learning (Borgland, Malenka, & Bonci, 2004). Other work has shown that chronic ethanol increases susceptibility to NMDAR-dependent LTD in VTA dopamine neurons (Bernier, Whitaker, & Morikawa, 2011). The latter effect involves at least 2 signaling systems including inositol trisphosphate (IP3) and protein kinase A. Taken together these findings support the idea that ethanol and other abused drugs induce their own forms of plasticity ("learning") in dopamine neurons, and that this may increase the probability of drug dependence.

Effects of ethanol on cerebellar plasticity

The cerebellum is involved in motor function and helps to control coordination, balance, and posture. This brain region is also involved in motor learning, and may participate in higher cognitive function. GABAergic Purkinje cells are principal neurons and their output regulates the function of deep cerebellar nuclei. Purkinje cell activity is modulated by several forms of synaptic plasticity at different glutamate inputs. LTD is particularly important in cerebellar activity and serves as an underpinning for specific forms of motor learning (Valenzuela, Lindquist, & Zamudio-Bulcock, 2010).

Peripheral inputs to the cerebellum arrive via the mossy fibers that make excitatory connections with glutamatergic granule cells. Granule cells in turn send excitatory inputs to Purkinje cells via the parallel fibers. Purkinje cells also receive excitatory inputs from the inferior olivary nucleus (ION) via the climbing fibers. Both parallel fiber and climbing fiber inputs exhibit robust LTD. Repeated concurrent activation of the parallel and climbing fibers with low frequency stimulation (e.g., 1 Hz × 5 min or more) results in parallel fiber LTD that has 3 temporal components, involving interactions among receptors and intracellular messengers (Ogasawara, Doi, & Kawato, 2008). Early parallel fiber LTD involves dual activation of AMPARs and mGluR1. mGluR1 acts via Gq-type G-proteins to activate phospholipase C-beta (PLCβ), which drives production of diacylglycerol and inositol 1,4,5-trisphosphate (IP3) to activate protein kinase C-alpha (PKCα) and stimulate release of calcium from intracellular stores (Aida et al., 1994). Transient receptor potential channels 1/3 (TRP 1/3) also contribute and help to activate voltage-gated calcium channels that provide a further calcium signal (Hartmann et al., 2008). Activation of PKC results in phosphorylation of GluA2 AMPAR subunits and internalization of AMPARs (Wang & Linden, 2000). An intermediate phase of parallel fiber LTD involves more persistent AMPAR endocytosis and results from activation of MAP kinase and phospholipase A2 (PLA2), with synthesis of arachidonic acid, activation of cyclooxygenase 2 (COX2), and production of prostaglandins D2 and E2 (Tanaka & Augustine, 2008). This second phase of LTD involves feedback that more persistently depresses AMPARs at these synapses. A late phase of parallel fiber LTD that persists for weeks or longer *in vivo* involves changes in protein synthesis (Linden, 1996).

Parallel fibers also exhibit a form of presynaptic LTP (Shibuki & Okada, 1992). This synaptic enhancement involves protein kinase A (PKA)-mediated phosphorylation of proteins involved in glutamate release from presynaptic terminals, including RIM-1α. A form of postsynaptic LTP involving insertion of AMPARs into synapses has also been described (Lev-Ram, Wong, Storm, & Tsien, 2002). Postsynaptic LTP results from 1 Hz stimulation of parallel fibers without concurrent activation of climbing fibers (Coesmans, Weber, De Zeeuw, & Hansel, 2004; Jörntell & Hansel, 2006).

Climbing fiber inputs onto Purkinje cells also exhibit LTD (Hansel & Linden, 2000). Here, repeated stimulation at 5 Hz for 30 sec results in persistent depression of AMPAR-mediated transmission. This form of LTD shares mechanisms with parallel fiber LTD and involves mGluR1, increases in intracellular calcium, and activation of PKC. Other modulators, including corticotrophin releasing factor, also participate.

Ethanol has long been known to depress cerebellar function, as manifested by motor incoordination and gait disturbances during acute intoxication. Longer-term alcoholism can result in chronic cerebellar dysfunction with persistent problems with coordination and gait, and cerebellar degeneration. Furthermore, ethanol impairs motor learning, and both parallel fiber and climbing fiber LTD are inhibited by ethanol (Valenzuela et al., 2010). While climbing fiber LTD may be more sensitive to ethanol than parallel fiber LTD, both are blocked acutely by 50 mM ethanol. Effects of ethanol on both forms of LTD are likely mediated by inhibition of mGluR1 and calcium channels (Belmeguenai et al., 2008; Su, Sun, & Shen, 2010). The greater sensitivity of climbing fiber LTD to ethanol may reflect greater potency of ethanol for inhibiting mGluR1-dependent signaling at these Purkinje cell inputs (Carta, Mameli, & Valenzuala, 2006). It is less certain, however, whether the block of LTD results from direct effects on mGluR1 or changes in complex downstream signaling pathways involved in cerebellar plasticity; effects on climbing fiber NMDAR inputs may also be involved (He, Titley, Grasselli, Piochon, & Hansel, 2013). Chronic effects of ethanol on cerebellar plasticity have been less extensively studied, but there are likely to be changes with repeated exposures that contribute to persistent dysfunction.

Ethanol and use-dependent plasticity of GABA synapses

We have focused on effects of ethanol on glutamate-mediated synaptic plasticity because these forms of plasticity have been most clearly linked to learning and memory and because mechanisms underlying these synaptic changes are reasonably well understood. There is also evidence that GABAergic synapses undergo long-term use-dependent forms of enhancement that modulate regional and interregional brain networks (referred to as LTP_{GABA}) (Nugent & Kauer, 2008). LTP_{GABA} involves heterosynaptic changes at GABA synapses evoked by activation of postsynaptic NMDARs followed by increases in presynaptic GABA release. While there is considerable information about effects of acute and chronic ethanol on GABA synapses, less information is available about LTP_{GABA}. In the VTA, Guan and He (2010) found that 40 mM ethanol acutely inhibited LTP_{GABA} by a mechanism involving mu (μ) opiate receptors. Interestingly, exposure to ethanol *in vivo* 1 day prior to the study also resulted in inhibition of LTP_{GABA}. How these changes affect behavior and learning are less certain, although changes in GABA plasticity in the VTA could influence drug-seeking behaviors and addiction. Several other abused drugs share ethanol's ability to dampen LTP_{GABA} in the VTA (Niehaus, Murali, & Kauer, 2010). In dorsolateral striatum, GABAergic inhibition also undergoes a form of persistent depression (a form of LTD_{GABA}) in rats exposed to intermittent ethanol (Adermark, Jonsson, Ericson, & Söderpalm, 2011).

Developmental ethanol exposure and long-term synaptic plasticity

Although alcoholism is largely a problem of adolescence and adulthood, children born to mothers who abuse alcohol during pregnancy can exhibit a cluster of features known as "fetal alcohol spectrum disorders" (FASD) (Valenzuela, Morton, Diaz, & Topper, 2012). Individuals with FASD, particularly those with the most severe form of the disorder, fetal alcohol syndrome (FAS), have a high incidence of cognitive problems, including deficits in learning and memory (Lebel et al., 2012; Streissguth et al., 1994). These individuals also have increased risk of developing major psychiatric disorders including substance use, mood

disorders, and psychotic disorders as they mature to adulthood (Famy, Streissguth, & Unis, 1998). Although mechanisms underlying FAS are incompletely understood, alcohol exposure during the early postnatal period in rodents, a time corresponding to late pregnancy and early postnatal life in humans, greatly increases apoptotic neuronal death throughout the CNS (Ikonomidou et al., 2000), and there is evidence that exposure of prenatal and neonatal rodents to ethanol results in diminished brain mass and loss of neurons in the hippocampus (Barnes & Walker, 1981). Ethanol-induced developmental apoptosis appears to result from combined effects on NMDARs and GABARs, and can be mimicked by other abused (Farber & Olney, 2003) and therapeutic drugs (Jevtovic-Todorovic et al., 2003). Agents that are particularly noxious are CNS depressants that dampen neural excitability during synaptogenesis (Mennerick & Zorumski, 2000).

Consistent with changes in hippocampal structure, early ethanol exposure alters hippocampal physiology as measured by changes in synaptic strength, inhibition, and short- and long-term forms of synaptic plasticity (Berman & Hannigan, 2000). Animals with developmental ethanol exposure also exhibit defects in hippocampal-dependent learning (Kim et al., 1997; Lilliquist, Highfield, & Amsel, 1999). A variety of alcohol delivery paradigms *in utero* or in the early postnatal development result in synaptic and behavioral changes. These include chronic exposures throughout pregnancy, shorter binge-like exposures, and even single-day exposures during the early postnatal period (Berman & Hannigan, 2000; Ikonomidou et al., 2000).

Early ethanol exposure is associated with changes in the expression of receptors that could contribute to defects in behavior and memory. In particular, exposure to high ethanol levels during development results in decreased NMDAR number and function (Costa, Savage, & Valenzuela, 2000). Interestingly, there is evidence that Mg^{2+} block of NMDA channels may be augmented by early ethanol, making it more difficult for these channels to participate in synaptic plasticity (Hughes, Kim, Randall, & Leslie, 1998; Morrisett, Martin, Wilson, Savage, & Swartzwelder, 1989). Early ethanol exposure also diminishes the function of PI-linked mGluRs and protein kinases (Mahadev & Vemuri, 1999; Perrone-Bizzozero et al., 1998; Queen, Sanchez, Lopez, Paxton, & Savage, 1993; Rhodes, Cai, & Zhu, 1994) that contribute to hippocampal synaptic plasticity. There is less information about longer-term changes in AMPA/kainate-type glutamate receptors. Some evidence suggests that GABA-mediated inhibition may be altered by early ethanol exposure with augmented effects of benzodiazepines and GABA-potentiating neuroactive steroids in the hippocampus later in life (Allan, Wu, Paxton, & Savage, 1998).

Although variable results are reported, hippocampal slices prepared from rodents treated with ethanol in the prenatal/early postnatal period show diminished ability to generate LTP in adolescence and adulthood (Bellinger, Bedi, Wilson, & Wilce, 1999; Chepkova et al, 1995; Izumi, Kitabayashi, et al., 2005b; Krahl, Berman, & Hannigan, 1999; Richardson, Byrnes, Brien, Reynolds, & Dringenberg, 2002; Swartzwelder, Farr, Wilson, & Savage, 1988; Tan, Berman, Abel, & Zajac, 1990; but see Titterness & Christie, 2012) and defects in hippocampal homosynaptic LTD (Izumi, Kitabayashi, et al., 2005b). Deficits in multiple transmitter systems likely contribute to these changes (Valenzuela et al., 2012) and some evidence suggests long-term changes in specific NMDAR subtypes, including dampened transmission mediated by GluN2B-expressing receptors (Izumi, Kitabayashi, et al., 2005b). Other work shows changes in GABAergic interneurons that contribute to defective brain network function (Miller, 2006; Zucca & Valenzuela, 2010). Early ethanol exposure also disrupts neurogenesis in the adult brain and this could contribute to learning and psychiatric problems as animals mature (Ieraci & Herrara, 2007). Interestingly, some studies in mice indicate that learning defects are more prominent in juveniles following early postnatal ethanol exposure and diminish with maturation to adulthood (Wozniak et al., 2004). How

this functional recovery occurs is uncertain, but likely reflects ongoing plasticity of the maturing brain.

While much work on early alcohol exposure has focused on changes in hippocampus, defects in synaptic plasticity and function affect multiple brain regions including neocortex, cerebellum, and striatum, among other areas (Valenzuela et al., 2012). A major concern in interpreting the existing literature and translating effects in rodents to humans is that studies vary considerably in timing of ethanol exposure and ethanol dose, with a number of studies using very high doses. Nonetheless, there is evidence that even moderate doses of ethanol during early development causes neuronal damage (Young & Olney, 2006) and has adverse effects on synaptic and behavioral outcomes (Valenzuela et al., 2012).

Summary and discussion

There is little doubt that ethanol impairs learning, memory, and other cognitive functions. While mechanisms underlying memory are not completely understood, available data support a role for long-term, use-dependent synaptic change, including LTP and LTD. These forms of plasticity are observed throughout the brain, although mechanisms underlying synaptic change can differ among regions. Evidence reviewed here indicates that ethanol has both acute and chronic adverse effects on learning-related plasticity across brain regions, and this likely contributes to cognitive dysfunction and disability. Effects of ethanol on synaptic plasticity are complex and depend upon the age of the animals, the dose and mode of ethanol administration, and the impact of ethanol withdrawal following chronic exposure. Sex and hormonal status are also likely important, but have received less systematic attention.

Ethanol's effects on learning-related plasticity involve multiple neurotransmitters and a host of receptors and intracellular and intercellular signaling systems (Lovinger & Roberto, 2013). Many of ethanol's effects on these systems are inhibitory, but it is also clear that some signaling pathways are activated by ethanol; this includes ethanol-induced stimulation of neurosteroids and other stress-related modulators. We have focused heavily upon ethanol's actions in the CA1 region of the hippocampus. In part this is because of the key role of the hippocampus in learning and memory, but also because numerous mechanistic studies have been conducted in this region. Thus, findings in the hippocampus are instructive for understanding ethanol's diverse actions, although effects in the hippocampus do not necessarily translate to all brain regions. Given the key role that NMDARs play in LTP and LTD, the ability of ethanol to block NMDARs is a natural starting point for describing effects on synaptic plasticity. As highlighted in Table 1, acute block of CA1 LTP typically involves high ethanol concentrations (usually 30 mM and above). At these concentrations, ethanol only partially inhibits NMDARs and may preferentially block a particular subtype expressing GluN2B subunits (Izumi, Nagashima, et al., 2005c). Similar degrees of NMDAR block by other antagonists, including subtype selective GluN2B antagonists, do not reproduce ethanol's effects on LTP, although GluN2B antagonists can block LTD. This has led to a search for other mechanisms and has raised the possibility that partial NMDAR antagonism may result in metaplastic actions as a result of glutamate's ability to stimulate residual unblocked NMDARs. Metaplastic changes, in turn, open up more complex intracellular signaling, including local production of GABA-enhancing neurosteroids within CA1 pyramidal neurons (Tokuda et al., 2011). Importantly, the facilitating effects of neurosteroids in LTP inhibition provide a model for considering how ethanol interacts with various stressors and other drugs (e.g. benzodiazepines) to impair memory. Stressful conditions or drugs that elevate neurosteroid levels would be expected to enhance the adverse effects of ethanol on LTP and learning, rendering ethanol more potent than in naïve tissue (Talani et al., 2011).

The findings with neurosteroids support the concept that glutamatergic neurons have the machinery to enhance their own GABAergic inhibitory responses in a paracrine or autocrine fashion when exposed acutely to certain stimuli or stresses (Tokuda et al., 2010). How this occurs with ethanol is not certain, but recent studies suggest that high concentrations of ethanol may be metabolized locally in the hippocampus to acetaldehyde, providing a trigger for neurosteroid synthesis and altered plasticity (Tokuda et al., 2013a, b). Given the known neurotoxicity of acetaldehyde (Correa et al., 2012; Quertemont et al., 2005), this raises an intriguing possibility – acute synaptic dysfunction in the context of severe ethanol intoxication, and perhaps memory blackouts themselves, may reflect homeostatic neuroprotective adaptations on the part of glutamatergic neurons. How the acute effects of ethanol relate to longer-term deleterious effects also remains uncertain, but such studies must account for ethanol-induced neurodegeneration in the mature brain.

We have focused on ethanol's ability to inhibit traditional models of synaptic plasticity. It is also clear, however, that ethanol induces its own lasting synaptic changes, and that these neuroadaptations likely contribute to addiction and to adverse psychiatric outcomes associated with alcoholism. Of note, a single *in vivo* administration of ethanol results in lasting synaptic changes in the VTA, reflecting a prominent drug effect on the brain's motivation system (Saal et al., 2003). Other work from McCool and colleagues (2010) highlights persistent LTP-like changes in the amygdala, consistent with the ability of ethanol to alter mood and anxiety. Understanding mechanisms underlying these changes could help in the development of more effective treatment and prevention strategies. Furthermore, it is possible to conceptualize alcoholism and other drug addictions as involving intertwined sets of neurocircuitry changes that initiate in the VTA-ventral striatal system (the point of attack of abused substances), and that progress over time to involve emotional and cognitive systems as these illnesses cycle through repeated bouts of intoxication, withdrawal, and chronic use, in the end becoming progressively more complex from a psychiatric perspective (Koob & Volkow, 2010). Thus, alcoholism, like other major psychiatric disorders, should be viewed as a neurocognitive illness reflecting, at least in part, drug-induced synaptic changes. In this scenario, adverse effects of ethanol on traditional learning-related synaptic plasticity outlined here are seen as contributing to illness progression by hampering the brain's ability to correct circuitry errors via new experiences and learning.

The current hope in psychiatry is to understand mental illnesses as disorders of neural networks (Zorumski & Rubin, 2011). Such efforts will be a major challenge in most psychiatric disorders. Because of the better-defined acute mechanisms of action of alcohol and other abused drugs, efforts to disentangle network dysfunction may be more tractable in substance use syndromes, providing instructive starting points for understanding the involvement of brain circuitry in other mental illnesses. Ultimately, prevention of persistent dysfunction and disability, including cognitive impairment, must be a therapeutic goal in order to dampen the public health impact of these illnesses.

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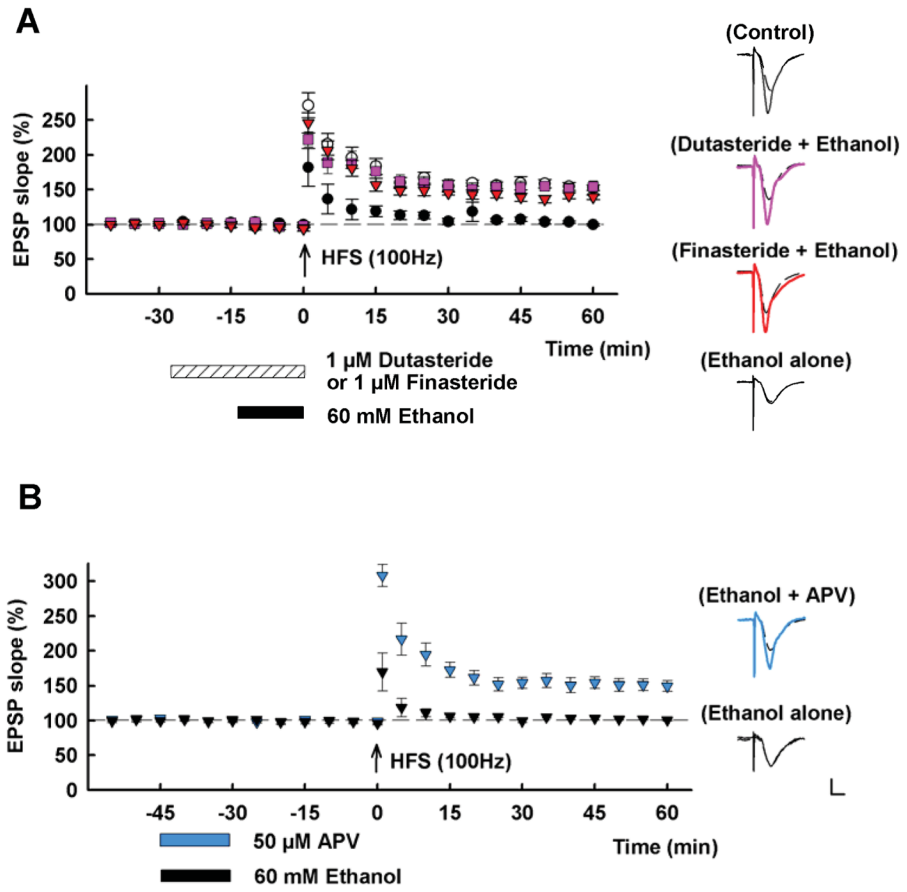

Figure 1.

This figure highlights several features of ethanol's acute effects on LTP in the CA1 region of hippocampal slices from P30 rats. A. The graph shows the ability of 60 mM ethanol administered for 15 min (black bar) to block LTP in the Schaffer collateral pathway (black circles). This LTP inhibition is overcome by pre-treatment with 1 μM finasteride (red triangles) or 1 μM dutasteride (purple squares). Finasteride and dutasteride block the synthesis of alloP and other 5α-reduced neurosteroids. Control LTP is shown in white circles. B. The graph shows that 60 mM ethanol inhibits LTP for at least 30 min following washout (black triangles) and that full block of NMDARs with 50 μM APV during ethanol administration overcomes LTP inhibition (blue triangles) when both drugs are washed out 30 min prior to high frequency stimulation (HFS, arrow; 100 Hz × 1 s tetanus). Traces to the right show EPSPs recorded during baseline (dashed traces) and 60 min following HFS (solid traces). Calibration: 1 mV, 5 ms. This figure is reproduced from Tokuda et al., *Journal of Neuroscience*, 2011.

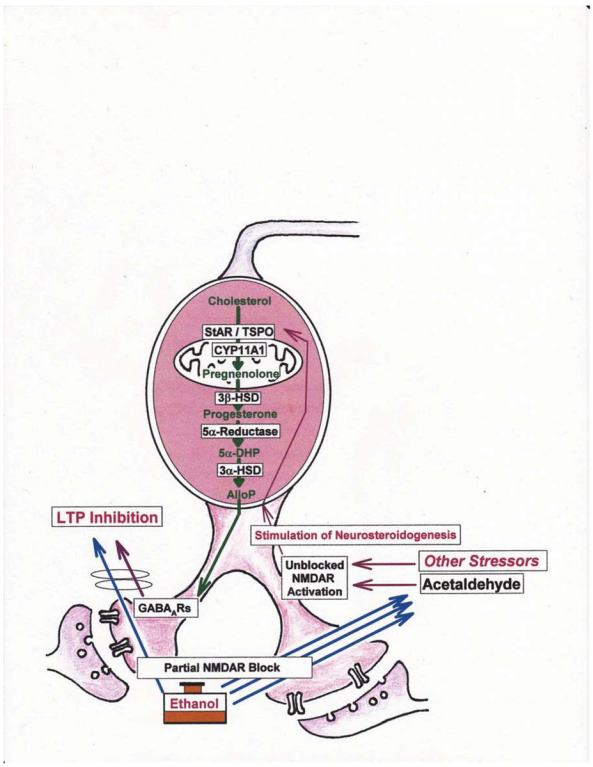

Figure 2.

The diagram depicts a scheme for acute block of LTP by ethanol in the CA1 region. Acute LTP inhibition requires high concentrations of ethanol (triple blue arrows) that partially inhibit NMDARs. Perhaps via local metabolism to acetaldehyde (Tokuda et al., 2013a, b; right side of figure), high concentrations of ethanol paradoxically promote activation of unblocked NMDARs, perhaps through elevation of glutamate levels. This untimely NMDAR activation, in turn, promotes local synthesis of GABA-enhancing neurosteroids (alloP) and enhanced $GABA_AR$ function, resulting in dampened LTP induction. The diagram also depicts key steps in the synthesis of alloP from cholesterol. The effects of high ethanol can be mimicked by lower ethanol in combination with exogenous alloP. The effects of low ethanol (single blue arrow) are not completely known, but include partial NMDAR antagonism (Izumi, Nagashima, et al., 2005c). Importantly, low ethanol alone does not enhance endogenous alloP production (Tokuda et al., 2011; left side of figure). Some actions of ethanol can be mimicked by other stressors that promote NMDAR activation. These include behavioral and metabolic stresses and can be mimicked, in part, by other drugs that enhance neurosteroid synthesis (Zorumski & Izumi, 2012). These latter conditions enhance the potency of ethanol to block LTP.

Table 1

Acute Ethanol & CA1 Hippocampal LTP *in vitro*

LTP Depressed or Blocked Completely						
Study	**Age**	**Ca/Mg**	**K**	**Stimulus**	**Intensity**	**[Ethanol]**
Blitzer (1990)	P50–90	2.5/1.5	5.0	100Hz × 1s × 2	10% max	5 mM
Sugiura (1995)	P56–63	2.4/1.3	6.2	100Hz × 0.5s	50% max	50–75 mM
Swartzw'r (1995)	P15–25	2.0/1.0	3.3	100Hz × .04s × 10	25% max	60 mM
Schummers (1997)	P40–60	2.5/1.0	5.0	100Hz × 1s or TBS	40–50% max	50 mM
Pyapali (1999)	P30	2.4/2.0	3.25	TBS	50% max	10–30 mM
Izumi (2005c)	P30	2.0/2.0	5.0	100Hz × 1 s	50% max	60 mM
Izumi (2007)	P30	2.0/2.0	5.0	100Hz × 1 s	50% max	40–60 mM
Fujii (2008)	~P120	2.5/2.0	5.0	100Hz × 0.25 s	40–60% max	8.6 mM
Tokuda (2011)	P30	2.0/2.0	5.0	100Hz × 1 s	50% max	60 mM

LTP Not Inhibited						
Study	**Age**	**Ca/Mg**	**K**	**Stimulus**	**Intensity**	**[Ethanol]**
Swartzw'r (1995)	P70–100	2.0/1.0	3.3	100Hz × .04s × 10	25% max	60 mM
Randall (1995)	P40–50	2.2/2.0	3.5	100Hz × 1s × 2	40% max	22 mM
Pyapali (1999)	P90	2.4/2.0	3.25	TBS	50% max	10–30 mM
Izumi (2005c)	P30	2.0/2.0	5.0	100Hz × 1 s	50% max	18 mM
Izumi (2007)	P30	2.0/2.0	5.0	100Hz × 1 s	50% max	20 mM
Fujii (2008)	~P120	2.5/2.0	5.0	100Hz × 0.25s	40–60% max	4.3 mM

Abbreviations: Age (animal age at which studies were done); P (postnatal day); Ca/Mg (concentrations of extracellular calcium and magnesium, in mM); K (extracellular potassium concentration, in mM); [Ethanol] (concentration of ethanol that was studied or that was required for significant effect on LTP); TBS (theta burst stimulation)

In some cases, the degree of LTP was diminished, but not completely blocked by this concentration of ethanol. In Schummers et al. (1997), TBS consisted of 100 Hz × 4 pulses × 10 every 0.2 s. In Izumi et al. (2007), 40 mM ethanol produced a partial block of LTP with complete block requiring 60 mM. Morrisett & Swartzwelder (1993) examined LTP n the dentate gyrus and found that 75 mM ethanol blocked LTP.