



REVIEW

Glutamate plasticity woven through the progression to alcohol use disorder: a multi-circuit perspective [version 1; referees: 2 approved]

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Abstract

Glutamate signaling in the brain is one of the most studied targets in the alcohol research field. Here, we report the current understanding of how the excitatory neurotransmitter glutamate, its receptors, and its transporters are involved in low, episodic, and heavy alcohol use. Specific animal behavior protocols can be used to assess these different drinking levels, including two-bottle choice, operant self-administration, drinking in the dark, the alcohol deprivation effect, intermittent access to alcohol, and chronic intermittent ethanol vapor inhalation. Importantly, these methods are not limited to a specific category, since they can be interchanged to assess different states in the development from low to heavy drinking. We encourage a circuit-based perspective beyond the classic mesolimbic-centric view, as multiple structures are dynamically engaged during the transition from positive- to negative-related reinforcement to drive alcohol drinking. During this shift from lower-level alcohol drinking to heavy alcohol use, there appears to be a shift from metabotropic glutamate receptor-dependent behaviors to N-methyl-D-aspartate receptor-related processes. Despite high efficacy of the glutamate-related pharmaceutical acamprosate in animal models of drinking, it is ineffective as treatment in the clinic. Therefore, research needs to focus on other promising glutamatergic compounds to reduce heavy drinking or mediate withdrawal symptoms or both.

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Introduction

Glutamate, the most prevalent excitatory neurotransmitter in the central nervous system, has long been associated with the excitotoxicity of alcohol withdrawal. Repeated episodes of alcohol withdrawal can generate aberrant behaviors such as hypermotility and increased seizures, which are classically thought to be related to an excitable state caused by increased glutamate action in the brain¹⁻⁴. These hyperglutamatergic periods of alcohol deprivation between heavy drinking events may be kindled across time, in a process like electrophysiological kindling⁵. Since this hypothesis is generally well accepted in the field, many have explored glutamatergic targets for new alcohol use disorder medications⁶. However, since an acute injection of ethanol also increases glutamate in the nucleus accumbens (NAc)⁷, a site heavily associated with both reward and stress, it suggests that there is a continuum of engagement through the transition from low to heavy drinking regulated by glutamate signaling. We focus on circuits that become recruited among subcortical structures beyond the classic mesolimbic-centric perspective.

There are distinct pharmacological classes of glutamate receptors, including ionotropic (iGluR) and metabotropic (mGluR) glutamate receptors and glutamate transporters that have been linked to a wide variety of alcohol-related phenotypes. In brief, iGluRs encompass α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors with 1–4 subunits (GluA1–4), N-methyl-D-aspartate (NMDA) receptors with two obligatory GluN1 subunits and combinations of GluN2(A–D) assemblies, and kainite receptors (GluK1–5). GluN receptors are more sensitive to alcohol than GluA and GluK⁸⁻¹⁰. Also, allosteric modulation of the GluN2B binding site can produce changes in alcohol-related behaviors. In contrast to the ligand-gated cation-selective ion channel iGluRs, mGluRs are G-protein-coupled and form three distinct classes: group I (mGluR1 and mGluR5), group II (mGluR2 and mGluR3), and group III (mGluR4, mGluR6, mGluR7, and mGluR8). Glutamate clearance in the synapse can be controlled by reuptake through transporters like excitatory amino acid transporters (EAATs) and adenosine transporters (equilibrative nucleoside transporter, or ENT) into glia and vesicular glutamate transporters into neurons. This review synthesizes the extant behavioral pharmacological findings for the role of glutamate, its receptors, and its circuitry throughout the brain in several stages of the transition to alcohol use disorder. In light of clinical literature, three general phases within alcohol use disorders are discussed: low-level drinking, binge drinking, and heavy drinking with withdrawal. We highlight specific animal behavior protocols in these three categories, but importantly these methods can be applied among all phases in the development of alcohol dependence.

Low-level drinking

Ethanol consumption that causes less than 0.08 g/dL (or 80 mg/dL) blood alcohol concentrations (BACs), less than 17 mM in the brain, is considered a low dose. Typical low-alcohol doses would be equivalent to a social drinker with BACs in the range of 0.015–0.025 g/dL (15–25 mg/dL). However, a BAC of 0.04 g/dL is classified as driving under the influence (DUI) for commercial drivers or previous DUI offenders (<http://www.dmv.org/>). With rodents that can readily metabolize alcohol, higher gram per kilogram (g/kg) alcohol concentrations may lead to BACs under 80 mg/dL.

Acute sub-intoxication doses of alcohol ingestion in humans can cause reduced strength of evoked field potentials in the prefrontal cortex (PFC), suggesting reduced excitability and functional connections¹¹. This is concordant with a 0.375 g/kg ethanol injection inhibiting PFC firing rate by approximately 20% versus baseline in anesthetized rats¹². In general, there is a paucity of clinical data for low-level alcohol consumption and glutamate activity because low-level drinkers are compared with heavy drinkers instead of abstinent people in clinical research.

Two-bottle choice

Two-bottle choice (2BC) involves offering the option to drink either a diluted ethanol-containing solution (concentrations range from 3 to 30%) or water for a fixed amount of time (Table 1). 2BC allows for the measurement of both voluntary consumption and ethanol preference over water and can be used as a single protocol or be combined with others to generate the desired level of drinking. In other words, first-day BACs may indicate low-level drinking, but weeks of 2BC could produce intoxicating BACs. This section focuses on 2BC studies that assess baseline ethanol preference, but daily limited-access studies that generate more binge-like drinking are discussed in the next section.

The studies are unequivocal that NMDA and AMPA regulate 2BC drinking, and both competitive and non-competitive GluN antagonists reduce 2BC intake¹³⁻¹⁵. For example, NMDA and AMPA infused into the lateral hypothalamus can both increase 2BC consumption¹⁴. However, GluN antagonists and glycine B site blockade can importantly reduce motor coordination to achieve these effects¹³⁻¹⁶. Similarly, GluN2A knockout mice show alcohol-induced impairments in motor coordination from wild-types (WTs) but do not show differences in consumption¹⁷. Other glutamate-related knockout lines also do not differ in 2BC drinking compared with WTs (for example, AMPA GluR1, GluN1 glycine, and mGluR5)¹⁸⁻²¹. Pharmacological manipulations of mGluRs, specifically mGluR5 antagonists and mGluR7 agonists, are effective at reducing 2BC intake in rats²²⁻²⁴. In complementary experiments, blockade with mGluR7 antagonist MMPiP or shRNA in the NAc can increase low-dose alcohol intake and preference^{24,25}. Since Homer2 knockout mice drink less than WTs in 2BC²⁶, it suggests that downstream signaling molecules are also important beyond glutamate receptor binding and clearance. It is worth mentioning that the US Food and Drug Administration (FDA)-approved medication for alcohol dependence, acamprosate, for which the glutamatergic mechanism of action is controversial, reduces 2BC drinking in rats²⁷. There is a glaring gap in the literature for which glutamatergic circuits in the brain may govern low-dose ethanol drinking. We need this critical information for insight into higher-dose plasticity.

Another important variable on the outcome of 2BC drinking and potential neuroadaptations is strain. Classic comparisons contrast between drinking behavior of C57BL/6J mice and DBA/2J mice, yet many inbred strains have been assessed for 2BC²⁸. Although specific sucrose-fading procedures can be used to induce ethanol drinking in DBA/2J mice (for example, 29) or bypassing ethanol taste altogether (for example, 30), this mouse strain drinks much less than C57BL/6J mice. 2BC preference may be related to strain

Table 1. Descriptions of alcohol-related protocols.

Method	Details	Ethanol g/kg achieved	Key references
Two-bottle choice (2BC)	3–20% ethanol given in one bottle with a secondary bottle of water usually for 24 hours	≤10 g/kg per 24 hours (mice)	McClearn and Rodgers ¹⁸³ ; Belknap, Crabbe, and Young ⁶⁴
Operant self-administration	9–15% ethanol (some add 2% sucrose) reinforcements are self-administered with cue for 30–60 minutes	≤90 mg/dL BAC (rats), ≤200 mg/dL BAC (mice); ≤1.5 g/kg per 30 minutes (rats), ≤3 g/kg per 1 hour (mice)	Elmer, Meisch, and George ⁸⁵ ; Melendez <i>et al.</i> ¹⁸⁶ ; Faccidomo <i>et al.</i> ⁵⁷
Cue-induced or stress-induced reinstatement	10–15% ethanol reinforcements are self-administered with cue, then extinction after cue is no longer paired with delivery of ethanol, finally reinstatement of ethanol-seeking behavior (lever pressing) occurs after ethanol-related cue or stressor is given	≤90 mg/dL BAC (rats), ≤200 mg/dL BAC (mice); ≤1.5 g/kg per 30 minutes (rats), ≤3 g/kg per 1 hour (mice)	Lê <i>et al.</i> ¹⁸⁷ ; Chaudhri <i>et al.</i> ¹⁸⁸ ; Shaham <i>et al.</i> ⁴⁶
Alcohol discrimination	Sucrose or food pellet reinforcement given upon pressing the correct response lever after ethanol or vehicle injection; test sessions involve injecting a novel drug and measuring lever selection	0.5–2 g/kg injection, intraperitoneally or <i>per os</i>	Grant ⁶⁴ ; Kostowski and Bienkowski ⁸⁵
Drinking in the dark	3 hours into the dark photoperiod, one bottle of 20% ethanol is given for 2–4 hours (mice)	≤3 g/kg per 2 hours; ≤7 g/kg per 4 hours (mice)	Rhodes <i>et al.</i> ⁹⁰ ; Thiele, Crabbe, Boehm ⁹¹
Scheduled high alcohol consumption	Water restriction for all but 90 minutes–10 hours, and every 3rd/4th day 5, 7, or 10% ethanol is substituted for 10–30 minutes followed by water	≤2 g/kg per 30 minutes; ≤100 mg/dL BAC (mice)	Finn <i>et al.</i> ¹⁰⁴ ; Tanchuk <i>et al.</i> ⁴⁴
Multiple scheduled access	Four 1-hour access periods to 15% and 30% ethanol separated by 2 hours starting 1 hour into dark cycle, 5 consecutive days/week	≤2 g/kg per 1 hour; ≤130 mg/dL BAC (rats)	Murphy <i>et al.</i> ¹⁰⁶ ; Bell <i>et al.</i> ¹⁰⁷ ; McBride <i>et al.</i> ¹⁰⁹
Alcohol deprivation effect	5–20% ethanol given every day for 6–8 weeks with a 3- to 6-day deprivation then resumption of drinking	Additional 2 g/kg per 24 hours over baseline (rats); additional 4 g/kg per 24 hours over baseline (mice)	Sinclair <i>et al.</i> ¹⁸⁹ ; Spanagel <i>et al.</i> ¹¹² ; Melendez <i>et al.</i> ¹⁹⁰
Intermittent access to alcohol	Every other day, 2BC of 20% ethanol and water is given for 24 hours, repeated for 4+ weeks	≤250 mg/dL BAC (rats), ≤200 mg/dL BAC (mice); ≤10 g/kg per 24 hours (rats); ≤25 g/kg per 24 hours (mice)	Wise ¹³¹ ; Simms <i>et al.</i> ¹³² ; Hwa <i>et al.</i> ¹³⁵ ; Carnicella, Ron, and Barak ⁵³
Chronic intermittent ethanol vapor	14-hour ethanol vapor and 10-hour air (rats) or 16-hour/8-hour (mice), repeated for 4+ weeks	150–250 mg/dL BAC during exposure; post-exposure, 6 g/kg per 24 hours (rats); ≤4 g/kg per 2 hours (mice)	Goldstein <i>et al.</i> ¹⁹¹ ; O'Dell <i>et al.</i> ¹⁹² ; Lopez and Becker ¹⁹³

Listed are popular animal protocols for alcohol drinking and the amount of alcohol given to the animal. These methods produce relevant blood alcohol concentrations (BACs) in rodents and are not restricted to a low, episodic, or heavy drinking category. Protocols can be repeated to generate the intended level of drinking or be combined for more exploration of the drinking behavior.

differences in the effect of glutamate and NMDA on the brain *in vitro*^{31,32} and differences in gene expression in response to acute ethanol³³. Also, alcohol-preferring (P) rats, genetically selected for high alcohol drinking, have a loss of the mGluR2 receptors that may contribute to escalated alcohol intake³⁴. Comparing high-drinking and low-drinking strains caused from trait selection or from inbred lines would increase the understanding of how glutamate-related genes influence drinking behavior.

Operant self-administration of alcohol

Operant self-administration is a powerful method for mice, rats, and monkeys to assess ethanol reinforcement. Via these methods, rodents will typically self-administer amounts ranging from 0.5 to 2 g/kg depending on factors such as session length, reinforcement schedule, and alcohol concentration by pressing a lever, spinning a wheel, or poking the nose into a receptacle (Table 1). Uncompetitive GluN antagonists ketamine and memantine reduce operant responding for ethanol with mechanistic target of rapamycin signaling, likely regulating the anti-alcohol effects of ketamine³⁵. Both mGluR5 and mGluR1 blockade and mGluR7-positive allosteric modulation decrease alcohol self-administration in rats and mice^{36–40}, particularly in the NAc^{41,42}. As in 2BC studies, some have seen ethanol-induced sedation and hypnosis with mGluR5 antagonist MPEP and mGluR2/3 antagonist LY341495⁴³ and non-specific reductions in sucrose self-administration^{39,44}. This may be due in part to mGluR5 influencing D1 receptors in seeking behavior⁴⁵.

Self-administration training techniques are also useful to investigate cue-induced reinstatement, or seeking behavior, following extinction of the alcohol-paired cues (Table 1). In operant self-administration protocols, cue-induced reinstatement or stress-induced reinstatement of alcohol seeking after a period of extinction training is also interpreted to be a form of relapse⁴⁶ (Table 1). We discuss the literature here instead of the relapse section, as no alcohol is consumed during reinstatement tests. There have been mixed reports for the ability of competitive GluN antagonists to affect reinstatement^{47,48}. For mGluRs, it is not surprising that mGluR5 antagonism and mGluR2/3 agonism reduce cue-induced reinstatement, alcohol seeking in Pavlovian spontaneous recovery, and enhanced sensitivity to the attenuation of conditioned reinstatement^{49–52}, but there are varying reports for whether these compounds affect baseline self-administration. Gass *et al.*⁵³ found evidence for increased glutamate transmission from the basolateral amygdala (BLA) to NAc core during cue-induced reinstatement of alcohol seeking. Glutamate transmission and transport may be mediated through adenosine ENT1⁵⁴ since N-acetylcysteine and ceftriaxone, which alter glial reuptake and release of glutamate, also alter alcohol self-administration⁵⁵. Downstream signaling molecules such as PKC ϵ , ERK, and CaMKII/AMPA in the PFC and amygdala have been well established in alcohol self-administration and cue-induced reinstatement^{56–59}. Specifically, amygdalar CaMKII/AMPA activation promotes self-administration and drinking^{60–62}, whereas inhibition of CaMKII in the PFC increases the positive reinforcing effects of alcohol⁶³. Others have explored the activation of mGluR2 amygdala to hippocampus pathway in cue-induced alcohol seeking, where mGluR-mediated synaptic depression is impaired in the hippocampus³⁴. It seems that subregions of the amygdala and also the PFC are recruited during this low-level drinking.

Alcohol-discriminative stimulus effects

Alcohol discrimination tasks are useful to assess the neurobiological mechanisms underlying the discriminative stimulus effects (for example, interoceptive effects) of low and high alcohol doses (Table 1). However, it is important to note that these tasks do not involve alcohol drinking but rather experimenter-administered alcohol. We have known for decades that the discriminative stimulus properties of ethanol are mediated by GluNs and GABAA^{64–66}. Specifically, lower alcohol doses (for example, 0.5–1 g/kg) engage GABA receptor systems whereas higher doses (>2 g/kg) involve NMDA receptor systems. Rats and cynomolgus monkeys can discriminate alcohol from glutamate release inhibitors and NMDA ligands, showing that they have partial alcohol-like effects^{67,68}. This is different from the discrimination of acamprosate, where acamprosate fails to substitute for an alcohol cue, suggesting that it is not a substitution drug⁶⁹. Besheer *et al.* have shown that alcohol discrimination is co-regulated by mGluR5 in the NAc and the mGluR2/3 in the amygdala^{70–73} and that inhibition of MEK/ERK(1/2) in the amygdala, but not NAc, potentiates the effects of a low alcohol dose⁷⁴. Recent work with stress hormone corticosterone links both mGluR5 and mGluR2/3 in the sensitivity to alcohol^{75,76}, suggesting a role for neuropeptide modulation of glutamatergic circuits. Furthermore, in addition to the NAc, a functional role for the medial PFC (mPFC) in modulating sensitivity to low alcohol doses has been shown^{66,77}. An interesting contribution from the Holmes lab shows that GluN2B in corticostriatal circuits governs choice learning and choice shifting⁷⁸. Although this learning is not in the presence of alcohol, they show a dissociation between OFC GluN2B in choice shifting and dorsal striatum GluN2B in choice learning. These findings suggest it is possible that learning about alcohol through discrimination tasks recruits distinct populations of both iGluR and mGluR in subcortical sites, although more research is required to confirm how this contrasts from habitual learning in the striatum.

Overall, there is ample evidence demonstrating PFC plasticity in alcohol-seeking behavior and low-dose alcohol drinking at a stage engaging positive reinforcement and the euphoric effects of the drug. Although 2BC studies have tested several facets of the glutamate system using knockout mice, there is a gap of knowledge in iGluRs in alcohol self-administration studies. This may be confounded by the fact that competitive GluRN antagonists mimic the interoceptive properties of alcohol. More recent studies have implicated GluRA in the rostromedial tegmental nucleus in alcohol seeking⁷⁹. Another behavioral outcome of low-dose acute, self-administered alcohol (1 g/kg) is an increase in inter-male aggression in a subset of mice⁸⁰. Memantine, neramexane, and mGluR5 antagonist MTEP interacted with alcohol to further increase alcohol-heightened aggression in mice, whereas mGluR2/3 agonist LY379268 did not⁸¹. CRF type-1 receptors regulate serotonin function from the dorsal raphe nuclei (DRN)-mPFC to alter alcohol-heightened aggression⁸², so glutamate may influence the mPFC for the expression of low-dose alcohol-related behavior.

Episodic drinking through binges and relapse

Binge drinking, defined as BACs greater than 0.08 g/dL or 80 mg/dL within 2 hours, is common among most strata of US adults and leads to an increased susceptibility for developing chronic alcoholism^{83,84}. This section focuses on hazardous, episodic,

binge drinking. However, epidemiological reports have found that there are almost as many binge-drinking episodes among moderate drinkers as among heavy drinkers in the US⁸³, so binge and relapse behavior represents the hazardous transition between moderate and heavy drinking. We focus on changes in glutamate plasticity to inform us on dramatic neurobiological events across species.

Binge alcohol drinkers have increased glutamate-to-creatine ratios and lower GABA concentrations in the anterior cingulate cortex (ACC) than do low alcohol drinkers^{85,86} presumably with glutamatergic perturbations. Repeated 2–3.4 g/kg alcohol injections increase accumbal and hippocampal glutamate compared with water-injected animals^{1,87,88}. This confirms a study in which young adults with depression had a positive correlation between the level of alcohol use and glutamate in the hippocampus⁸⁹.

Drinking in the dark

The prototypical procedure in mice to induce binge-like drinking is giving one bottle of alcohol, offered 3 hours into the active dark photoperiod for 2–4 hours, termed drinking in the dark (DID) (Table 1)^{90,91}. C57BL/6J mice typically drink 2–5 g/kg in a session. Even two alcohol “binges” in adolescent rats are sufficient to abolish long-term synaptic depression in hippocampal slices and to evoke cognitive deficits via a short-lasting, repeated blockade of GluN, inducing a change in the receptor subunit composition⁹². An earlier DID study showed that both acamprosate and MPEP decreased DID intake without affecting sugar or water drinking⁹³. Others have gone on to show that mGluR5 signaling affects PKC ϵ in the NAc or central amygdala (CeA) to regulate DID^{94,95}. Specifically, repeated DID for 30 days elevates CeA levels of glutamate-associated proteins of Homer2a/b, mGluR1a, GluN2B, and PLC ϵ 24 hours after withdrawal from binge drinking⁹⁵. Intra-CeA and intra-NAc mGluR1 negative allosteric modulator JNJ-16259685 also reduces DID intake^{96,97}. More recent studies have isolated downstream factors after DID such as mGluRs affecting AMPA receptor trafficking proteins like eukaryotic elongation factor 2 or decreased amygdalar CaMKII α T286 phosphorylation^{98,99}. Importantly, this effect was isolated to the amygdala but not NAc or dorsal striatum. This may be related to the lack of difference in frequency and amplitude of spontaneous excitatory post-synaptic current (sEPSC) in dorsolateral striatum and dorsomedial striatum medium spiny neurons between 6 weeks’ DID and water-drinking mice¹⁰⁰. Also, moving away from the classic mesolimbic pathway, others have identified a novel ventral tegmental area (VTA)–bed nucleus of the stria terminalis (BNST) CRF circuit in DID¹⁰¹. CRF-R1 antagonists can reduce DID through intact CRF-R2 signaling, and inhibiting VTA-projecting BNST CRF neurons reduces DID¹⁰¹. Repeated 2 g/kg alcohol injections result in enhanced GluN-mediated LTP in VTA dopamine neurons¹⁰², so it is likely that this VTA–BNST glutamate pathway is altered during binge drinking in DID in a similar fashion.

Beyond DID, there are other daily limited-access procedures that lead to binge drinking in rodents. Permutations of DID exist, such as 2-hour daily access for 14 days in C57BL/6J mice, to study other facets of binge-like drinking, such as tolerance¹⁰³. The scheduled high alcohol consumption (SHAC) protocol involves water restriction for all but 90 minutes of water access, and every fourth day alcohol replaces water for 10–30 minutes¹⁰⁴. Systemic

administration of mGluR5 antagonist MPEP decreases SHAC intake but also sucrose self-administration⁴⁴. Further studies have found a role for mGluR5–Homer2–PI3K signaling in the NAc in SHAC intake¹⁰⁵, which can be replicated in the DID protocol⁹⁴. Another limited-access protocol is multiple scheduled access (MSA), in which P rats are offered four 1-hour 2BC sessions separated by 2 hours across the dark cycle 5 days per week¹⁰⁶. Changes in gene expression in the NAc and amygdala after weeks of MSA drinking in P rats have been extensively studied^{107–109}, so what is needed is targeting how glutamate interacts between the sites through mGluRs and iGluRs¹¹⁰. MSA can lead to a transient increase in alcohol drinking after a weekend of deprivation¹⁰⁷, an alcohol deprivation effect (ADE), so it incorporates episodic drinking in both limited-access binge drinking and relapse-like drinking.

Alcohol deprivation effect

Relapse is also episodic in nature, both in the clinic and modeled with animals. Relapse, a hallmark of alcohol use disorders, is the resumption of drinking following a prolonged period of abstinence. With animals, experimenters can model relapse through the expression of the ADE. In this method, alcohol-drinking animals are deprived of alcohol for a period of time (for example, days to weeks), and then following this deprivation period, an escalation in alcohol drinking is observed following re-exposure to alcohol (Table 1). Intra-PFC glutamate and acamprosate separately reduce the ADE^{111,112}. However, many other glutamatergic compounds—GluN/glycine receptor antagonist L-701,324, GluN2B selective antagonist ifenprodil, GluN channel blocker neramexane, GluA/GluK antagonist CNQX, and Na⁺ channel blocker lamotrigine—attenuate the ADE similar to alcohol seeking during cue-induced reinstatement^{47,48}. To the best of our knowledge, there are no reports for the involvement of iGluR or mGluR circuitry in the ADE, but we hypothesize that it would be similar to plastic changes in DID or operant self-administration circuitry.

It appears that episodic drinking, the amorphous transition between low-dose and high-dose intake, engages both reward-related and stress-related glutamate brain processes. A single DID protocol is mGluR5 antagonist-responsive, whereas repeated DID for a month alters changes in downstream glutamate proteins. Multiple glutamatergic compounds reduce the ADE and cue-induced reinstatement, so perhaps these protocols in combination with others would be more apt for screening medications for the clinic.

Heavy drinking and withdrawal

Heavy drinking is defined as consuming five or more drinks on the same occasion on each of five or more days in the past month¹¹³. People who exhibit heavy drinking may or may not fall into the category of mild, moderate, or severe alcohol use disorder on the basis of the accompanying psychological symptoms¹¹⁴. As mentioned earlier, heavy drinking can be different across species. Most clinical literature focuses on alcoholics, whereas rodent studies do not have the commodity of an overarching term. For example, heavy drinking in outbred rats can be 6 g/kg per day, whereas in mice it may be 15 g/kg per day. The subsequent analysis considers heavy drinking and withdrawal for the particular species.

Tsai *et al.*¹¹⁵ originally reported that alcohol-dependent patients have increased glutamate and glycine in the cerebrospinal fluid

during withdrawal, with accompanying reduced GABA concentrations. With proton magnetic resonance spectroscopy, increased glutamate levels have been associated with more years spent drinking, loss-of-control alcohol use, and craving during detoxification in heavy drinkers or non-treatment-seeking alcoholics^{116–118}. This glutamate dysfunction is localized to the NAc and the ACC with a positive correlation between craving and glutamate and glutamine in these regions^{118,119}. GluN compounds like ketamine, memantine, and d-cycloserine mimic the subjective effects of alcohol in recovering alcoholics^{120–122}. However, it is unfortunate that clinical trials with memantine or FDA-approved acamprosate did not prevent relapse compared with placebo in alcohol-dependent patients in large-scale double-blind experiments^{123–127}. In a massive genetics study, Schumann *et al.*¹²⁸ reported that genetic variations in GluN2A have the greatest relevance for human alcohol dependence among 10 glutamatergic probe genes, yet increased GluN2B expression and GluN2C in the ACC and dorsolateral PFC during withdrawal can indicate likelihood of alcohol craving and risk for relapse^{129,130}. It appears that the ACC is a distinct site for glutamate plasticity in heavy drinking.

Intermittent access to alcohol

Cycles of bingeing and withdrawal occur in the transition to developing an alcohol use disorder. We can model voluntary alcohol drinking in between periods of abstinence, or alcohol deprivation, with 24-hour intermittent access to 2BC alcohol^{131–133}. Weeks of intermittent alcohol access can lead to drinking despite adverse consequences¹³⁴ and signs of withdrawal such as handling-induced convulsions and decreased social interactions^{135,136}. Giving access to alcohol for a 24-hour period may cause variability in when animals choose to drink, so researchers can also measure fluid consumption during the initial 2-, 4-, and/or 6-hour access within the 24-hour period. With this, front-loading behavior may be observed accompanied by high BACs after 2-hour access (Table 1)¹³⁵. Additionally, smaller segments within 24-hour access allow drug manipulations to be assessed^{137,138}.

Acamprosate reduces intermittent alcohol drinking in rats but not continuous-access alcohol drinking¹³². Confirming clinical reports, outbred mice drinking on intermittent access to alcohol for 8 weeks show increased extracellular glutamate in the mPFC during withdrawal compared with 1 week of drinking and compared with water drinkers¹³⁶. Early reports with intermittent-access drinking in rats, drinking 7 g/kg per day, have enhanced post-synaptic GluA function in VTA neurons in the absence of any change in pre-synaptic glutamate release¹³⁹. Similarly, glutamatergic and GABAergic synaptic transmission are altered in the striatum of non-human primates with extended access for 3 years¹⁴⁰. Six months of continuous access and intermittent access to alcohol consumption in P rats produce selective increases in group I mGluR/Homer2/GluN2 expression within the NAc core and CeA^{141,142}. Intermittent alcohol can produce short-term increases in Homer/glutamate receptor expression within both the NAc core and the CeA, which may increase the aversion of early alcohol withdrawal and consequently augment the negative reinforcing properties of alcohol. Modulators of the glutamate transporters reduce heavy drinking on a continuous-access schedule (15% and 30% ethanol) in P rats and the increased extracellular glutamate compared with water drinkers¹⁴³. These P rats also have enhanced expression of glutamate transporters EAAT2/GLT1

and xCT in the NAc and PFC, suggesting a role for targeting glutamate uptake in heavy drinking¹⁴⁴. Long-term intermittent alcohol recruits GABA and CRF neurons in the mPFC during withdrawal and disconnects the PFC–CeA pathway, suggesting that dysregulation of mPFC interneurons may be an early index of glutamate/GABA neuroadaptation in alcohol dependence¹⁴⁵. Impaired executive control over motivated behavior accompanies negative reinforcement during withdrawal. Seif *et al.*¹⁴⁶ show that cortical activation of NAc hyperpolarization-active GluN mediates aversion-resistant intermittent alcohol intake. Both the mPFC to NAc core and insula to NAc core mediate both quinine- and footshock-resistant alcohol drinking on an intermittent-access schedule. It appears that corticolimbic sites are integral to glutamate plasticity caused by chronic intermittent drinking.

Withdrawal from chronic intermittent ethanol vapor and other forced alcohol methods

There are several other protocols that forcibly induce a post-dependent state in animals, such as repeated high-dose alcohol injections, alcohol liquid diet, and chronic intermittent ethanol (CIE) vapor exposure (Table 1). Studies on brain glutamate during alcohol withdrawal have been most extensively explored using these methods, since they surpass the aversive taste of alcohol drinking solutions to induce heavy BACs. However, it is important to note that CIE is used to render rodents ethanol-dependent to subsequently increase voluntary ethanol intake, not only to maintain high BACs^{147–149}. Microdialysis studies have shown increased glutamate in the striatum¹⁵⁰, NAc^{87,151–153}, and hippocampus^{1,154} during withdrawal in alcohol-exposed rats and mice. These results are similar to 5 g/kg alcohol gavage injections for 2–4 weeks causing increased glutamate in striatum, hippocampus, and substantia nigra 8–12 hours after the last ingestion¹⁵⁵. To counteract excitotoxicity, acamprosate and GluN antagonists have been used to decrease alcohol drinking and to alleviate symptoms of alcohol withdrawal, including increased glutamate tone and convulsive events^{112,151,156–158}. It is important to note that pharmacologically increasing glutamate transmission in the NAc with TBOA, a glutamate reuptake inhibitor, can increase drinking in both non-dependent and CIE-dependent mice¹⁵³. Alternatively, decreasing glutamate transmission in the NAc by activating group II mGluRs reduces drinking, although the effect was stronger in dependent mice. These results comparing glutamate in non-dependent and dependent animals have similar directionality with different magnitudes, so there may be separate but overlapping actions in the NAc for treating drinking versus withdrawal symptoms with glutamatergic compounds.

In accordance with clinical studies, the PFC is a large target of glutamate plasticity in alcohol dependence. CIE results in increased GluN-mediated activity in the mPFC and increased GluN1 and GluN2B subunit expression^{159,160}. Mice that show “compulsive-like” behaviors after CIE exhibit increased NMDA currents in the orbitofrontal cortex compared with air-exposed controls¹⁶⁰. Rescue of infralimbic PFC mGluR2 deficit restores control over alcohol-seeking behavior¹⁶¹. It appears that mGluR2 and mGluR5 can target symptoms of withdrawal (but see¹⁶²). Acamprosate improved attention set-shifting of alcohol-exposed animals but did not alter the concurrent changes in synaptic transmission or membrane excitability of mPFC neurons, indicating that the changes are not the pharmacological targets of acamprosate in the recovery of mPFC

functions¹⁶³. Abulseoud *et al.*¹⁶⁴ showed that attenuation of alcohol withdrawal by ceftriaxone induced upregulation of glutamate transporter EAAT2. Reduction of EAAT2 likely contributes to a hyperglutamatergic state in the ENT1 knockout mice^{54,165,166}. Some have suggested that increasing glutamate uptake through transporters has a potential therapeutic role in the treatment of alcohol dependence¹⁶⁷ (but see¹⁶⁸). Aberrations in PFC function entangle reduced executive control and poor decision making in alcoholics¹⁶⁹.

The extended amygdala—composed of the BNST, BLA, and CeA—is particularly vulnerable to glutamate plasticity caused by CIE treatment. Chronic alcohol exposure produces neuroadaptations in glutamatergic transmission in the CeA^{170,171}, and GluN2B-containing GluNs are most sensitive to CIE^{170,172,173}. CIE, but not continuous vapor exposure, increases BNST GluN-mediated EPSCs, not from altered glutamate release but from an increase in GluN2-containing GluN¹⁷⁴, suggesting that repeated cycles of exposure and withdrawal are necessary for these adaptations to occur. CIE enhances long-term potentiation formation in the BNST in GluN2B knockout mice through extrasynaptic GluN¹⁷⁵. Stress-induced alterations in anxiety-like behavior were absent following bilateral infusion of GluK1 agonist ATPA into the BLA, which augmented BLA GABAergic neurotransmission, and stress increased the amplitude of sEPSC and miniature inhibitory post-synaptic current¹⁷⁶. A regulatory stress neuropeptide could be nociceptin, since nociceptin application decreases glutamate transmission and blocks alcohol-induced effects in the CeA of naïve and CIE rats, but nociceptin antagonist revealed tonic inhibitory activity of nociceptin on evoked CeA glutamatergic transmission only in alcohol-dependent rats¹⁷⁷. Changes in the extended amygdala indicate a transition from positive reinforcement to negative

reinforcement as stress neuropeptides like nociceptin, CRF, and dynorphin are more engaged¹⁷⁸.

Together, chronic forced or voluntary access to alcohol affects glutamate in multiple subcortical sites like the PFC and extended amygdala, and this agrees with the clinical literature. In addition to these sites, many others have examined the hippocampus as a crux of CIE-induced glutamatergic changes. Group I mGluRs and GluN2B-containing GluNs in CA1 and cortex impair LTD, reduce spine density, and disrupt learning^{179,180} (but see 138). This may be related to the enhanced stress systems recruited during repeated exposure to and withdrawal from alcohol. In line with this hypothesis, corticohippocampal GluN2B is engaged during repeated swim stress¹⁸¹. This circuitry is also recruited in other addictive disorders. Glutamate homeostasis is a mediator of long-term drug-seeking behavior, especially through disruptions of the cysteine/glutamate exchanger and EAAT2/GLT1¹⁸². Alterations in glutamate transmission after chronic alcohol exposure and withdrawal are evident, but some effects are also likely to be unique to withdrawal alone. Future research can tease apart these dynamic distinctions or suggest that they are interconnected.

Discussion

Across all phases of alcohol drinking, glutamate is a critical regulator of subcortical plasticity in the brain. We have mapped some relevant regions of interest according to their involvement in low, moderate, or heavy drinking (Figure 1), but more work can be done to study how these sites work on a circuit level. Downstream signaling factors like CaMKII are important in the PFC and amygdala in operant self-administration. Binge drinking in the DID protocol also affects mGluR5 in the CeA and CRF in the BNST

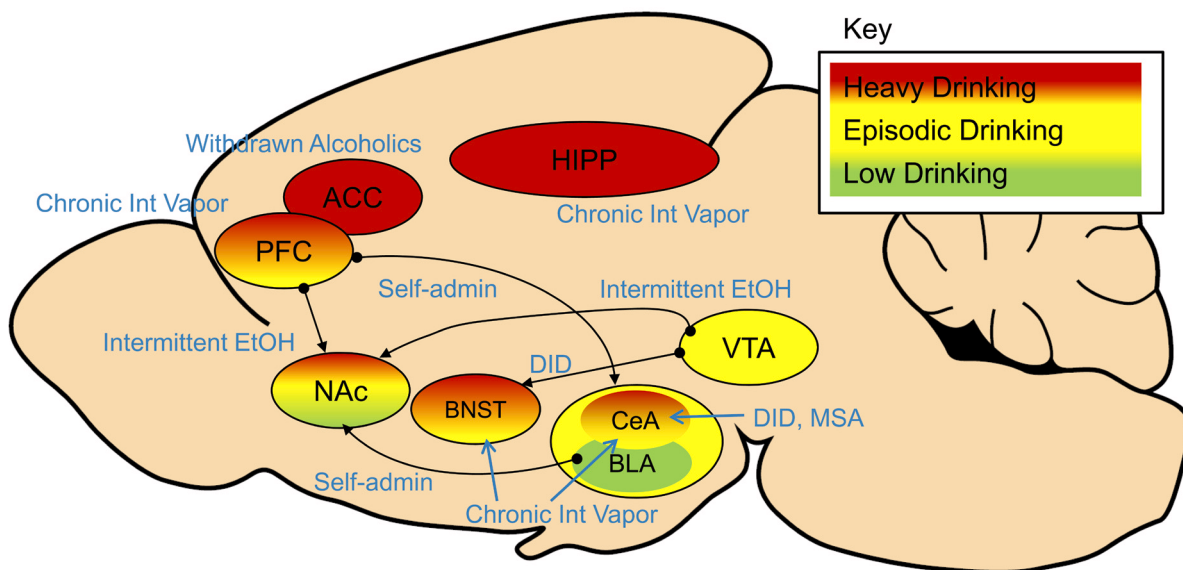


Figure 1. A sagittal representation of subcortical structures and their circuitry related to different stages during the transition from low-level drinking to heavy alcohol use. Regions of interest in red indicate involvement in heavy drinking, yellow in episodic drinking, and green in lower-level drinking. Known connections start with the black circle and finish with the black arrowhead. Animal drinking protocols are depicted in blue italics. ACC, anterior cingulate cortex; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CeA, central amygdala; HIPP, hippocampus; NAc, nucleus accumbens; PFC, prefrontal cortex; VTA, ventral tegmental area.

in connection with mesolimbic targets. Glutamate in the ACC and PFC is heavily disrupted in alcoholics, which is supported by preclinical research using intermittent access to alcohol or CIE. Electrophysiological studies also reveal a role for GluN2 in the extended amygdala in alcohol withdrawal, related to negative affect. Furthermore, glutamate transmission in circuits stemming from the NAc represents an overlap in circuitry from light to episodic to heavy drinking in a limited-access model. The roles of glutamate transporters and the interaction with glia are better understood at both ends of the drinking spectrum (2BC and CIE), but more can be learned through intermediate protocols that reveal the transition to heavy drinking. Overall, there appears to be a shift from mGluR-dependent behaviors to GluN-related processes transitioning from lower-level alcohol drinking to heavy alcohol drinking. The efficacy of acamprosate in animal models of drinking is high, in sharp contrast to its ineffective treatment in the clinic. Therefore, research needs to focus on other promising glutamatergic compounds to reduce heavy drinking or mediate withdrawal symptoms or both.

Author contributions

LSH conceptualized the review, wrote the first draft of the manuscript, edited the writing, and agreed to the final content. TLK conceptualized the review, edited the writing, and agreed to the final content. JB edited the writing and agreed to the final content.

Competing interests

The authors declare that they have no competing interests.

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