TABLE 3 Compounds targeting glutamatergic neurotransmission in alcohol seeking behavior

Receptor target	Compound	Pharmacological class	Seeking behaviour	Drug administration	Subjects	References
NMDAR	Viral-knockdown of GluN2C-NMDA		(-) chained schedule of reinforcement	Systemic	Wistar rats	Seif et al. (2013)
NMDAR	Ifenprodil	Antagonist	(-) Priming reinstatement	DMS	Sprague Dawley rats	Wang et al. (2010)
NMDAR	MK–801	Antagonist	(0) Cue-Induced Reinstatement	Systemic	Long Evans rats	Bäckström & Hyytiä, (2004)
NMDAR	CGP39551	Antagonist	(0) Cue-Induced Reinstatement	Systemic	Long Evans rats	Bäckström & Hyytiä, (2004)
GluN2B-NMDA	Ro25–6981	Antagonist	(-) Habitual alcohol seeking	OFC	Long Evans rats	Morrisot et al. (2019b)
GLUN2B	Acamprosate	Antagonist	(-) Cue-Induced Reinstatement	Systemic	Wistar rats	Bachteler et al. (2005)
GLUN2B	Neramexane	Antagonist	(0) Cue-Induced Reinstatement	Systemic	Wistar rats	Bachteler et al. (2005)
NMDA/glycine R	L–701,324,	Antagonist	(-) Cue-Induced Reinstatement	Systemic	Long Evans rats	Bäckström & Hyytiä, (2004)
AMPA/kainate	CNQX	Antagonist	(-) Cue-Induced Reinstatement	Systemic	Long Evans rats	Bäckström & Hyytiä, (2004)
AMPA	Aniracetam	PAM	(+) Cue-Induced Reinstatement	Systemic	Alcohol-preferring (P) rats	Cannady et al. (2013)
AMPA/kainate	CNQX	Antagonist	non-reinforced extinction session.	pVTA	Long Evans rats	Czachowski et al. (2012)
AMPA/kainate	NBQX	Antagonist		BLA	Long Evans rats	Sciascia et al. (2015)
mGluR5	CDPPB	PAM	(-)extinction of alcohol-seeking behavior	Systemic	Wistar rats	Gass et al. (2017)
mGluR5	MTEP	NAM	(-) Cue-Induced Reinstatement	BLA, Nac	Wistar rats	Sinclair et al. (2012)
mGluR5	MPEP	NAM	(-) Cue-Induced Reinstatement	Systemic	Alcohol-preferring (P) rats	Schroeder et al. (2008)
mGluR5	CDPPB	PAM	(-)extinction of alcohol-seeking behavior	Systemic	Wistar rats	Cannady, Fisher, et al. (2017)
mGluR5	CDPPB	PAM	(-)extinction of alcohol-seeking behavior / (-) Cue-induced Reinstatement	Systemic	Wistar rats	Gass et al. (2014)
mGluR5	MTEP	NAM	(+)extinction of alcohol-seeking behavior	IfL	Wistar rats	Gass et al. (2014)
mGluR5	MTEP	NAM	(-)extinction of alcohol-seeking behavior	PrL	Wistar rats	Gass et al. (2014)
mGluR2	↑mGluR 2/3 expression		(-) Cue-Induced Reinstatement	IL-Nac	Wistar rats	Meinhardt et al. (2013)
mGluR2	AZD8529	PAM	(-) Cue-Induced Reinstatement / (0) stress-induced reinstatement	Systemic	Wistar rats	Augier et al. (2016)

(Continues)

TABLE 3 (Continued)

Receptor target	Compound	Pharmacological class	Seeking behaviour	Drug administration	Subjects	References
mGluR2/3	LY379268	Agonist	(-) Cue-Induced Reinstatement	Systemic	Long Evans rats	Bäckström & Hyytiä, (2005)
mGlu8	(S)−3,4-DCPG	Agonist	(-) Cue-Induced Reinstatement	Systemic	Long Evans rats	Bäckström & Hyytiä, (2005)
mGluR2/3	LY379268	Agonist	(-) Cue-Induced Reinstatement	Systemic	Wistar rats	Kufahl, Martin-Fardon, & Weiss, (2011)
mGluR2/3	LY379268	Agonist	(-) stress-induced reinstatement	Systemic	Wistar rats	Sidhpura, Weiss, & Martin-Fardon, (2010)
mGluR5	MTEP	NAM	(-) stress-induced reinstatement	Systemic	Wistar rats	Sidhpura, Weiss, & Martin-Fardon, (2010)
mGluR2/3	LY379268	Agonist	(-) Cue-Induced Reinstatement / (-) stress-induced reinstatement	Systemic	Wistar rats	Zhao et al. (2016)
mGlu4/mGlu7	LSP2−9166	Agonist	(-) Priming reinstatement after forced absinence	Central (i.c.v.)	Long Evans rats	Lebourgeois et al. (2018)

(-) Decrease; (+) Increase; (0) No effect.

Alcohol acutely dampens mGluR1/5 function, but protracted alcohol use potentiates both the expression and activity of these receptors (Zorumski et al., 2014). Using a drug discrimination procedure, it was shown that activation of accumbal mGluR5s is essential for interoceptive effects of alcohol (Besheer et al., 2009). Accordingly, competitive mGluR5 antagonists as well as mGluR5 negative allosteric modulators (NAMs) attenuate cue-induced reinstatement of alcohol seeking, both when administered systemically, and when microinjected into the NAc or the BLA (Bäckström et al., 2004; Caprioli et al., 2018; Sinclair et al., 2012). Using the selective mGluR5 NAM 2-Methyl-6-(phenylethynyl)pyridine (MPEP), it was shown that suppressed reinstatement of alcohol seeking following down-regulated mGluR5 transmission involves the extracellular signal-regulated kinases 1/2 ($ERK_{1/2}$) signaling pathway (Schroeder et al., 2008). $ERK_{1/2}$ signaling is downstream of mGluR5, and is activated in amygdala inputs to the ventral striatum by contingent presentation of alcohol associated cues. Within this circuitry, $ERK_{1/2}$ phosphorylation was associated with increased cue-induced reinstatement of alcohol seeking, and this effect was counteracted by MPEP (Schroeder et al., 2008).

A potential interpretation of these findings is that mGluR5s are involved in associative learning that links alcohol-associated cues with alcohol effects, becomes progressively strengthened over the course of developing alcohol addiction, persists into protracted abstinence, and contributes to alcohol seeking under non-reinforced conditions. In addition to blocking the recall of these alcohol-memories as reviewed above, facilitating their extinction may also offer treatment opportunities. Exposure-based extinction of alcohol cue-reactivity is a clinical treatment of alcohol addiction, but its efficacy is limited (Mellentin et al., 2017), and could potentially be strengthened using medications. In that context, the mGluR5 PAM CDPPB (3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide) has been shown to facilitate extinction of cue-conditioned alcohol seeking (Gass et al., 2014). This effect was mediated through mGluR5 modulation of small-conductance calcium activated potassium (K_{Ca}^2) channels, and was obtained both with systemic and intra-infralimbic/PFC activation of mGluR5s (Cannady, McGonigal, et al., 2017).

In contrast with mGluR5, mGluR1 effects on alcohol seeking have not been extensively studied, with most of the literature focusing on mGluR1 PAMs and NAMs effects on alcohol consumption (Besheer et al., 2008; Cozzoli et al., 2014; Lum et al., 2014).

mGluR2-mediated control of glutamatergic neurotransmission through presynaptic modulation of glutamate release has received considerable interest as a pharmacological target in several psychiatric disorders (Crupi et al., 2019). Prolonged alcohol exposure has been shown to disrupt mGluR2 function by down-regulating expression of *Grm2*, the gene encoding this receptor. Deficits in corticostriatal and cortico-amygdala mGluR2-mediated feedback inhibition of glutamate release have been shown to promote reinstatement of alcohol seeking (Lovinger & McCool, 1995; Meinhardt et al., 2013). High levels of glutamate in the BLA and NAc have been detected during cue-induced reinstatement of alcohol seeking, together with an alcohol-induced mGluR2 down-regulation in mPFC (Gass et al., 2011; Meinhardt et al., 2013). Genetically selected alcohol-preferring P rats lack mGluR2s, and show escalation of alcohol consumption and resistance to alcohol drinking devaluation (Timme et al., 2020; Zhou et al., 2013).