Pharmacology, Biochemistry and Behavior 199 (2020) 173058

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Review

Neural mechanisms underlying incubation of methamphetamine craving: A mini-review

Rachel D. Altshuler, Hongyu Lin, Xuan Li*

Department of Psychology, University of Maryland College Park, College Park, MD 20742, United States of America

ARTICLE INFO

Keywords:
Addiction
Methamphetamine
Incubation of craving
Relapse
Circuit
Molecular

ABSTRACT

Cue-induced drug craving and seeking progressively increases during abstinence. This "incubation of drug craving" phenomenon has been observed in both laboratory animals and humans. Preclinical studies identified several neural mechanisms underlying incubation of drug craving after forced abstinence, primarily focusing on cocaine. Recently, studies started focusing on another powerful psychostimulant, methamphetamine (Meth), and developed new incubation procedures (choice-induced and punishment-induced abstinence). Here, we review mechanistic studies at the circuit, synaptic and molecular levels on incubation of Meth craving. First, we provide an overview of neural adaptations associated with prolonged forced abstinence after extended-access Meth self-administration. Next, we review studies examining the causal roles of discrete brain regions and associated circuits, glutamate transmission, histone deacetylase 5 and oxytocin in incubation of Meth craving after forced abstinence. Lastly, we review causal and correlational studies examining the mechanisms underlying incubation of Meth craving after choice-induced voluntary abstinence and punishment-induced abstinence, respectively. We conclude by discussing the translational potential of these mechanistic studies in Meth relapse prevention in human drug users.

1. Introduction

Methamphetamine (Meth) is a powerful psychostimulant and currently no approved pharmacological treatments are available for Meth addiction (Morley et al., 2017). A major obstacle for treating drug addiction, including Meth, is relapse during abstinence (Brecht and Herbeck, 2014; Sinha et al., 2011; Hunt et al., 1971), often triggered by re-exposure to drug-associated cues (O'Brien et al., 1992). To account for this persistent relapse, Gawin and Kleber (1986) proposed that cue-induced cocaine craving progressively increases during the early weeks of abstinence and remains high over prolonged abstinence. In the early 2000s, an analogous incubation phenomenon was identified in rats, termed incubation of drug craving, based on the findings that cocaine and heroin seeking progressively increases after forced abstinence from drug self-administration (Grimm et al., 2001; Shalev et al., 2001). Subsequent studies demonstrated that incubation of drug craving also occurs in rats with a history of Meth (Shepard et al., 2004; Theberge et al., 2013), alcohol (Bienkowski et al., 2004), nicotine (Abdolahi et al., 2010) and sucrose (Grimm et al., 2005) self-administration. Moreover, incubation of drug craving in rats is contributed by both discrete and contextual drug cues, with discrete cues potentiating the non-reinforced operant responding (Adhikary et al., 2017). From a clinical perspective, this incubation phenomenon mimics relapse after forced abstinence, such as incarceration or hospitalization (Reichel and Bevins, 2009), and has been demonstrated in humans across multiple drug classes, including cocaine (Parvaz et al., 2016), alcohol (Treloar Padovano and Miranda Jr, 2020; Li et al., 2015a), nicotine (Bedi et al., 2011) and Meth (Wang et al., 2013).

Over the last two decades, several groups have identified neural mechanisms underlying incubation of drug craving after forced abstinence, primarily focusing on cocaine (Pickens et al., 2011; Wolf, 2016; Loweth et al., 2014a; Li et al., 2015b). While early studies had investigated changes of dopaminergic functions in the mesolimbic system associated with prolonged abstinence after extended-access Meth self-administration (Shepard et al., 2006; Krasnova et al., 2010), it was only five years ago when we and others began to examine the causal roles of distinct neural mechanisms underlying incubation of Meth craving (e.g., Li et al., 2015c; Li et al., 2018a; Scheyer et al., 2016). Furthermore, modified incubation procedures were developed to investigate neural mechanisms underlying incubation of Meth craving after choice-induced (food or social interaction) voluntary abstinence (Caprioli et al., 2015; Venniro et al., 2018) and after punishment-induced and forced abstinence (Krasnova et al., 2014) (hereafter shortened to punishment-induced abstinence). These procedures mimic

---

* Corresponding author.
E-mail address: annali@umd.edu (X. Li).

https://doi.org/10.1016/j.pbb.2020.173058
Received 12 August 2020; Received in revised form 27 September 2020; Accepted 9 October 2020
Available online 23 October 2020
0091-3057/ © 2020 Elsevier Inc. All rights reserved.

Box 1
Glossary of behavioral and biological terms.

Behavioral terms	
Choice-induced (food or social interaction) voluntary abstinence	An abstinence procedure developed to model contingency management therapy (Roll, 2007). Rats are first trained to self-administer an alternative reward (food or social interaction), followed by Meth. The delivery of alternative reward and drug is paired with its respective discrete cues (e.g., tone and light). After training, rats undergo daily mutually exclusive choice procedures between alternative reward and Meth. Caprioli et al. (2015) and Venniro et al. (2018) demonstrated that during choice procedures, rats prefer alternative reward over drug, and therefore achieve choice-induced voluntary abstinence.
Conditioned-place preference	A Pavlovian conditioning procedure measuring the rewarding effects of drugs by determining preference for a drug-associated environment
Contingency management	A behavioral therapy that uses non-drug rewards (e.g., token) or punishments to promote abstinence in humans (Roll, 2007).
Forced abstinence	An abstinence procedure in which rats simply return to their home cages after self-administration training, with no access to the operant chamber.
Incubation of drug craving	Time-dependent increases in cue-induced drug seeking following withdrawal (Grimm et al., 2001).
Punishment-induced and forced abstinence	An abstinence procedure to model voluntary abstinence imposed by adverse consequences, a phenomenon observed in humans (Epstein and Preston, 2003; Katz and Higgins, 2003; Burman, 1997; Klingemann, 1991). Rats are first trained to self-administer Meth paired with a discrete cue. After training, rats undergo the daily punishment sessions, during which 50% of responses on the active lever and Meth infusions are paired with a foot shock (Krasnova et al., 2014). Krasnova et al. (2014, 2017) demonstrated that during the punishment phase, self-administration decreases in a subset of rats (shock-sensitive rats), achieving punishment-induced abstinence. In contrast, a subset of rats continues Meth self-administration despite of the shock (shock-resistant rats). After the punishment phase, incubation of drug craving occurs in both shock-resistant and shock-sensitive rats after a period of forced abstinence, with higher drug seeking behavior in shock-resistant than shock-sensitive rats during both early and prolonged withdrawal.
Reinstatement	A procedure modeling relapse behaviors and testing for a reemergence of drug seeking behavior after the behavior has been previously extinguished. The reinstatement of drug seeking behavior can be elicited by drug-associated cues, non-contingent drug exposure, or stress.
Biological terms	
Ca^{2+}-permeable AMPA receptor	A type of AMPA receptors that lack of GluA2 subunits. Unlike GluA2-containing AMPA receptors, GluA2-lacking AMPA receptors are calcium permeable, and exhibit greater conductance, inward rectifying currents and a unique pharmacological profile (e.g., blocked by polyamine drugs, such as Naspm).
Cocaine-and-amphetamine-regulated transcript prepropeptide	A neuropeptide that is differentially expressed in the striatum when a rat is injected with cocaine or amphetamine (Douglass et al., 1995). CARTpt modulates stimulant-induced behaviors such as locomotor activity (Kuhar et al., 2005).
Histone deacetylase 5	Class II histone deacetylase responsible for removing acetyl groups from the N-terminal tail of histones.
mGlu1-mediated synaptic depression	A type of synaptic depression expressed postsyanptically in response to activation of mGlu1, which leads to endocytosis CP-AMPA receptors.
Oxytocin	A neuropeptide hormone with anxiolytic effects
Positive allosteric modulator	Ligands that bind to an allosteric binding site on a receptor, resulting in an increased agonist affinity or efficacy at the receptor

relapse in humans after cessation of contingency management (Roll, 2007; Silverman et al., 2012), which employs either non-drug rewards or negative consequences associated with drug use (Epstein and Preston, 2003; Katz and Higgins, 2003).

In this review, we discuss neural mechanistic studies at the circuit, synaptic and molecular levels on incubation of Meth craving after forced abstinence, choice-induced voluntary abstinence and punishment-induced abstinence in the past decade. In addition, we discuss similarities and differences in neural mechanisms between incubation of Meth and cocaine craving after forced abstinence. We also compare neural mechanisms underlying incubation of Meth craving after forced abstinence and choice-induced voluntary abstinence. Note that unless specified, all studies discussed below used male rats. A glossary of terms used in this review is in Box 1.

2. Neural mechanisms underlying incubation of Meth craving after forced abstinence

Most studies so far have focused on examining neural mechanisms underlying incubation of Meth craving after forced abstinence. Among these, several studies built on prior knowledge on incubation of craving to other drugs, primarily cocaine, and demonstrated either similar or distinct neural mechanisms. Below we first describe main findings from correlational studies that examined neural adaptations associated with prolonged withdrawal (beyond 24 h) from extended-access Meth self-administration (6 h or more/d), and refer readers for further details summarized in Table 1. Note that studies combining correlational and causal investigations in incubation of Meth craving are discussed in subsequent sections. Additionally, we focus on studies using extended-access self-administration because of the early observations that incubation of craving is more robust after extended than short (e.g., 2 h/d) access self-administration training (Lu et al., 2004). Next we describe studies that examined the causal roles of discrete brain regions and associated circuits, glutamate transmission, epigenetic mechanisms and oxytocin in incubation of Meth craving. We summarize these findings and list parallel cocaine studies in Table 2.

2.1. Neural adaptations associated with prolonged withdrawal from extended-access Meth self-administration

Early studies began focusing on dopaminergic pathways, but together with later findings, yielded conflicting results. Shepard et al. (2006) combined *in situ* hybridization with Western blotting and reported that tyrosine hydroxylase (TH) mRNA and protein expressions in ventral tegmental area (VTA) and substantia nigra compacta (SNC) increase on withdrawal day 1 but not 30. On either withdrawal days, dopamine transporter (DAT) mRNA levels in VTA and SNC, or TH protein and DAT mRNA levels in nucleus accumbens (NAc) and dorsal striatum (DS) exhibit no change. A recent study also reported an increase of DAT, but not TH or dopamine 2 receptor (D2R) protein expression in striatum on withdrawal day 3 (D'Arcy et al., 2016).

In contrast, Krasnova et al. (2010) used high performance liquid chromatography (HPLC) with electrochemical detection and reported persistent decrease of dopamine (DA) levels in rat striatum on withdrawal day 1, 7 and 14, as well as decreased DA levels in cortex on withdrawal day 14. Authors also observed decreased TH and DAT protein expressions in both rat striatum and cortex on withdrawal day 14. McFadden et al. (2012) reported decreased dopamine uptake and

Table 1
Neural adaptations beyond 24-h withdrawal from extended access Meth self-administration.

Brain region	SA procedure (dose)	Withdrawal day	Technique	Specific molecular targets	Major findings	Citation
Forced abstinence						
SNC/VTA	9 h/d x 10 d (0.1 mg/kg/inf)	WD 30	ISH	*DAT*	−/−	Shepard et al., 2006
				TH	−/−	
			WB	TH	−/−	
CPu			WB	TH	−	
NAc					−	
SN					−	
Striatum	8 h/d x 7 d (0.06 mg/ml/inf)	WD 30	[^{3}H]DA uptake assay	DAT	▼	McFadden et al., 2012
				VMAT2	−	
	8 h/d x 7 d (0.12 mg/ml/inf)			DAT	▼	
	8 h/d x 7 d (0.24 mg/ml/inf)		WB	DAT	▼	
DS	1 h/d x 6 d, then 6 h/d × 22 d (0.05 mg/kg/0.1 ml inf)	WD 3	WB	DAT	▲	D'Arcy et al., 2016
				TH	−	
				D2R	−	
Striatum	15 h/d × 8 d (0.1 mg/kg/inf)	WD 7/14	HPLC analysis	DA	▼/▼	Krasnova et al., 2010
				DOPAC	▼/−	
				HVA	▼/−	
				NE	−/−	
				5-HT	▲/−	
				5-HIAA	−/−	
		WD 7	WB	GFAP	▲	
		WD 14	WB	TH	▼	
				DAT	▼	
				5-HTT	−	
Cortex		WD 7/14	HPLC analysis	DA	−/▼	
				DOPAC	−/−	
				NE	−/−	
				5-HT	−/−	
				5-HIAA	−/−	
		WD 7	WB	GFAP	▲	
		WD 14	WB	TH	▼	
				DAT	▼	
				5-HTT	−	
DS	15 h/d × 8 d (0.1 mg/kg/inf)	~WD 30	HPLC analysis	DA	▼	Krasnova et al., 2013
				DOPAC	−	
			qPCR/WB	*Drd1*/D1R	−/−	
				Drd2/D2R	−/▼	
				cfos /cFos	−/▼	
				Fosb/FosB	−/−	
				ΔFosb/ΔFosB	−/▼	
				Bdnf/BDNF	−/▼	
				Trkb/TrkB	−/▼	
			WB	CREB	▼	
				pCREB	▼	
			ChIP	H3K4me3	−	
DS	9 h/d x 10 d (0.1 mg/kg/inf)	WD 2/35 (whole cell extracts) /WD30-50 (Fos-positive cells)	qPCR (whole cell extracts for WD2/35, compared with saline; Fos-positive cells for WD 30-50 relapse tests, compared with Fos-negative cells in Meth rats)	*Bdnf*	−/−/▲	Li et al., 2015d
				TrkB	−/−/▲	
				Gria1	−/−/▲	
				Gria2	−/−/▼	
				Gria3	−/−/▲	
				Grin1	−/−/−	
				Grin2a	−/−/▲	
				Grin2b	−/−/−	
				Grm1	−/−/▲	
				Grm5	−/−/−	
				Hdac1	−/−/−	
				Hdac2	−/−/−	
				Hdac3	−/−/▲	
				Hdac4	−/−/▲	
				Hdac5	−/−/▲	
				Sirt1	−/−/−	
				Sirt2	−/−/−	
				Crebbp	−/−/−	
				Suv39h1	−/−/−	
				G9a	−/−/−	
				GLP	−/−/▲	
				Kdm1a	−/−/▲	
				Mil1	−/▲/−	
				Dnmt3a	−/−/▲	

(*continued on next page*)

Table 1 (*continued*)

Brain region	SA procedure (dose)	Withdrawal day	Technique	Specific molecular targets	Major findings	Citation
CeA	9 h/d × 10 d (0.1 mg/kg/inf)	WD 2/35	RNA-seq	DEGs	– (215) /▲ (2217)	Cates et al., 2018
OFC					▲ (118) / – (55)	
			qPCR	*Dcn*	▲/▼	
				Col3a1	▲/▼	
				Henmt1	–/–	
NAc	3 h/d × 20d (0.1 mg/kg/inf)	WD 30	qPCR (male/female rats)	*Pdyn*	▲/–	Daiwile et al., 2019
				Hcrtr1	–/–	
				Hcrtr2	▼/▼	
				Crh	▼/▼	
				Crhr1	–/–	
				Crhr2	▲/–	
				Avp	▼/–	
				Avpr1a	▼/▼	
				Avpr1b	▼/▼	
DMS/AIT	6 h/d x 10 d (0.1 mg/kg/inf)	WD 30 (after the 2-h relapse test)	qPCR (Fos-positive cells, different from Fos-negative cells)	*Bdnf*	–/–	Li et al., 2019
				TrkB	▲/▲	
				Gria1	–/–	
				Gria2	–/–	
				Gria3	▲/–	
				Grin1	▲/▲	
				Grin2a	–/–	
				Grin2b	▲/–	
				Grm1	▲/–	
				Grm5	–/–	
				Hdac1	–/–	
				Hdac2	–/–	
				Hdac3	▲/–	
				Hdac4	–/–	
				Hdac5	▲/▲	
				Sirt1	–/–	
				Sirt2	–/–	
				Crebbp	▲/–	
				Suv39h1	–/–	
				G9a	–/–	
				GLP	–/–	
				Kdm1a	–/–	
				Mll1	–/–	
				Dnmt3a	–/–	
PRh	1 h/d x 7 d, then 6 h/d x 14 d (20 μg/50 μl/inf)	WD 8/14	WB	mGlu2/3	–/–	Reichel et al., 2011
				mGlu5	–/▼	
HPC				mGlu2/3	–/–	
				mGlu5	–/–	
PFC		WD 8		mGlu2/3	–	
				mGlu5	–	
PFC	1 h/d x 7 d, then 6 h/d × 14 d (20 μg/50 μl/inf)	WD 14	WB (* surface, # total)	mGlu2/3	▼*	Schwendt et al., 2012
				mGlu7	▼*	
NAc				mGlu2/3	▼*#	
				mGlu7	–	
DS				mGlu2/3	▼*#	
				mGlu7	–	
PRh/HPC/PFC	1 h/d x 7 d, then 6 h/d x 14 d (20 μg/50 μl/inf)	WD 7	WB	GluN1	–/–/–	Reichel et al., 2014
				GluN2a	–/–/–	
				GluN2b	▼/–/–	
PRh	1 h/d x 7 d, then 6 h/d x 14 d (20 μg/50 μl/inf)	WD 7	Capillary electrophoresis	GluN1 (surface)	–	Scofield et al., 2015
				GluN1 (intracellular)	–	
				GluN2b (surface)	▼	
				GluN1 (intracellular)	–	
mPFC/HPC/PRh	1 h/d x 7 d, then 6 h/d × 14 d (20 μg/50 μl/inf)	WD 7	WB	5HT2A	▲/–/▲	Hamor et al., 2018
				mGlu2	–/–/–	
				Gq	▲/–/▲	
				Gi	–/–/–	
				Go	–/–/–	

(*continued on next page*)

Table 1 (*continued*)

Brain region	SA procedure (dose)	Withdrawal day	Technique	Specific molecular targets	Major findings	Citation
NAc	6 h/d x 10 d (0.1 mg/kg/inf)	WD 3/21/48	WB	GluA1 (surface)	–/–/–	Murray et al., 2019
				GluA1 (total)	–/–/–	
				GluA2 (surface)	–/–/–	
				GluA2 (total)	–/–/–	
				GluA3 (surface)	–/–/–	
				GluA3 (total)	–/–/–	
				mGlu1 (surface)	–/–/–	
				mGlu1 (total)	–/–/–	
				Homer1b/c	–/–/–	
				Homer2	–/–/–	
		WD 30	Puromycin IP	GluA1	▲	
				GluA2	–	
mPFC	1 h/d x 7 d, then 6 h/d × 14 d (20 µg/50 µl/inf)	WD 8	Electrophysiology (sEPSCs)	AMPA/NMDA	▼	Mishra et al., 2017
				PPR	–	
				Avg. frequency	–	
				Avg. amplitude	–	
				NMDA (current amplitude)	▲	
				AMPA (current amplitude)	–	
			Capillary electrophoresis	GluN2b	▲	
NAc			Electroph7ysiology (sEPSCs)	PPR	▼	
				Avg. frequency	▲	
				Avg. amplitude	–	
PL	6 h/d x 14 d (0.05 mg/kg/inf)	WD 9-14	Electrophysiology (sEPSCs, males/females)	Amplitude	–/–	Pena-Bravo et al., 2019
				Frequency	–/–	
				Rise	–/–	
				Decay	–/–	
			Electrophysiology (eEPSCs, males/females)	Amplitude	–/▲	
				Decay	▼/–	
				NMDA current	–/▲	
HPC	1 h/d x 8-10 d, then 6 h/d × 22d (0.05 mg/kg/inf)	WD 29	IHC	BrdU	–	Recinto et al., 2012
				Ki-67	▲	
				Fos	–	
mPFC/NAc				Fos	–/–	
<u>Punishment-induced abstinence</u>						
NAc/Striatum	9 h/d x 20 d (0.1 mg/kg/inf)	WD 35 (5 d punishment, 30 d forced abstinence)	qPCR (SR) (*relative to yoked-SR shock saline control, # relative to no-shock saline control)	*Oxt*	▲*#/–	Krasnova et al., 2017
				OxtR	▲#/–	
				CARTpt	–/▲*#	
				FMO2	–/▼*	
				PDK4	▼*▲#/▼*#	
				PTPRO	▼*/▼*	
			qPCR (SS) (*relative to yoked-SS shock saline control, # relative to no-shock saline control)	*Oxt*	–/–	
				OxtR	▲#/–	
				CARTpt	–/–	
				FMO2	–/–	
				PDK4	▲#/–	
				PTPRO	▲#/–	

(*continued on next page*)

Table 1 (*continued*)

Brain region	SA procedure (dose)	Withdrawal day	Technique	Specific molecular targets	Major findings	Citation
DS	9 h/d x 22 d (0.1 mg/kg/inf)	WD 43 (13 d punishment, 30 d forced abstinence)	PCR array (SS relative to SR)	*Bdnf*	▲	Torres et al., 2018
				Gdnf	–	
				Ngf	▲	
				Vgf	▲	
				Ntf3	▲	
				Trka	–	
				Trkb	–	
				Gfra1	▲	
				Gfra2	▲	
				Ngfr	–	
				Crh	▲	
				Crhr1	▲	
				Crhr2	–	
				Crhpb	▲	
				Ucn	–	
			qPCR (SR/SS) (relative to saline control)	*Bdnf*	–/▲	
				Ngf	–/–	
				TrkA	–/▼	
				TrkB	–/–	
				Gfra2	–/▲	
				Crh	–/–	
				Crhr1	–/▲	
				Crhr2	–/–	
				Crhbp	–/▲	
				Ucn2	–/▲	
				Cfos	▲/▲	
				Fosb	–/–	
				Egr1	▲/–	
				Egr2	▲/–	
				Egr3	–/–	
			WB (SR/SS) (relative to saline control)	proBDNF	▼/▼	
				mature BDNF	▲/▲	
				TrkB	–/–	
				pTrkB	–/–	
				proNGF	–/–	
				mature NGF	▲/▲	
				TrkA	–/–	
				pTrkA	–/▲	
				p75NTR	–/▲	
				Sortilin	–/–	
				pc-Raf	–/–	
				pMek1/2	▲/▲	
				pErk1/2	–/–	
				pMSK1	–/▲	
				pCREB	–/▲	
				pmTOR	–/▲	
				H3ac	–/▲	
				pMeCP2	–/▲	
OFC➔DMS	9 h/d x 20 d (0.1 mg/kg/inf)	WD 35 (5 d punishment, 30 d forced abstinence)	fMRI (SR/SS) (compared to saline control)	Resting state functional connectivity	–/–	Hu et al., 2019
PL➔VLS					–/–	

Comparisons are made in reference to saline controls unless otherwise stated in the table.

Abbreviations: 5-HIAA: 5-hydroxyindoleacetic acid; 5-HT: 5-hydroxytryptamine; CeA: central amygdala; CPu: caudate putamen; DA: dopamine; DAT: dopamine transporter; DMS: dorsomedial striatum; DOPAC: 3,4-dihydroxyphenylacetic acid; DS: dorsal striatum; HPC: hippocampus; HVA: homovanillic acid; GFAP: glial fibrillary acidic protein; mPFC: medial prefrontal cortex; NAc: nucleus accumbens; NE: norepinephrine; OFC: orbitofrontal cortex; PFC: prefrontal cortex; PL: prelimbic cortex; PRh: perirhinal cortex; SN: substantia nigra; SNC: substantia nigra pars compacta; SR: shock resistant; SS: shock sensitive; TH: tyrosine hydroxylase; VLS: ventrolateral striatum; VTA: ventral tegmental area; IHC: immunohistochemistry; DEG: differentially expressed genes; ISH: *in situ* hybridization; ChIP: chromatin immunoprecipitation; HPLC: high performance liquid chromatography; EPSC: excitatory postsynaptic currents; eEPSC: evoked EPSC; sEPSC; spontaneous EPSC; IP; immunoprecipitation; PPR: paired-pulse ratio; WB: western blot; WD: withdrawal day. Symbols: (▲): increase; (▼): decrease; (–): no change

DAT protein expression in striatal tissue on both withdrawal day 8 and 30, but with no changes of DA levels or TH protein expression. Krasnova et al. (2013) later extended their previous findings and found sustained decrease in dorsal striatal DA after 1-month withdrawal. This is accompanied with decreased protein expressions of D2R [but not dopamine 1 receptor (D1R)], transcription factors [ΔFosB, cFos, cAMP response element protein (CREB) and phosphorylated CREB (pCREB)], brain-derived neurotrophic factor (BDNF) and tyrosine kinase B receptor (TrkB) in DS.

The main factor that contributes to the inconsistent results above is the daily Meth dose during self-administration. For example, the Meth intake in studies from Krasnova et al. (2010, 2013) was about 15 mg/kg/d, more than doubled than those in other studies (Shepard et al., 2006; D'Arcy et al., 2016; McFadden et al., 2012). Therefore, neural adaptations observed by Krasnova et al. (2010, 2013) are possibly due to neurotoxic effect of Meth. Indeed, authors reported increased protein expression of glial fibrillary acidic protein (GFAP, a cellular marker for astrocytes) in both striatum and cortex on withdrawal day 7 (Krasnova et al., 2013). In contrast, no changes of GFAP protein expressions across cortical and striatal areas are detected in rats with an average Meth

Table 2
Neural mechanisms underlying incubation of methamphetamine craving and parallel studies on incubation of cocaine craving.

Site of manipulation	Manipulations	SA procedure (dose)	Withdrawal day	Behavioral outcomes	Citation	Parallel incubation studies with cocaine
Forced abstinence						
dmPFC	Mus + Bac (0.03 + 0.3 nmol/0.5 µl/side); 15 min before relapse tests	9 h/d x 10 d (0.1 mg/kg/inf)	WD 30	–	Li et al., 2015c	Koya et al., 2009; Ma et al., 2014
vmPFC				–		Koya et al., 2009; Ma et al., 2014; Miller et al., 2017
OFC				–		NA
NAc core	Naspm (40 µg/0.5 µl/side); 15 min before relapse tests	6 h/d x 10 d (0.1 mg/kg/inf)	WD 45	▼	Scheyer et al., 2016	Loweth et al., 2014b; Conrad et al., 2008
DS	SCH23390 (0.75 µg/1 µl/side);15 min before relapse tests	9 h/d x 10 d (0.1 mg/kg/inf)	WD 2	–	Li et al., 2015d	NA
			WD 30	▼		
	HDAC5 overexpression; AAV-mHDAC5 injections before SA training		WD 2	–	Li et al., 2018b	
			WD 30	▲		
	HDAC5 knockdown; AAV-shHDAC5 injections before SA training		WD 2	–	Li et al., 2018b	
			WD 30	▼		
DMS/DLS	SCH23390 (0.75 µg/1 µl/side); 15 min before relapse tests	9 h/d x 10 d (0.1 mg/kg/inf)	WD 30	▼	Li et al., 2015d	NA
	HDAC5 knockdown; AAV-shHDAC5 injections before SA training		WD 2	–	Li et al., 2018b	
			WD 30	–		
BLA	Mus + Bac (0.03 + 0.3 nmol/0.5 µl/side); 15 min before relapse tests	9 h/d x 10 d (0.1 mg/kg/inf)	WD 2	–	Li et al., 2015c	Lee et al., 2013
			WD 30	–		
CeA	Mus + Bac (0.03 + 0.3 nmol/0.5 µl/side); 15 min before relapse tests	9 h/d x 10 d (0.1 mg/kg/inf)	WD 2	–	Li et al., 2015c	Lu et al., 2005; Lu et al., 2007
			WD 30	▼		
	CeL SOM knockdown; AAV-shSOM injections before SA training	6 h/d x 12 d (0.1 mg/kg/inf)	WD 1	–	Venniro et al., 2020	
			WD 15	▼		
AIT-L	Mus + Bac (3 + 15 ng/0.3 µl/side); 15 min before relapse tests	6 h/d x 10 d (0.1 mg/kg/inf)	WD 30	▼	Li et al., 2018a	NA
AIT-M				–		
AIT➔DMS	Mus + Bac (AIT-L; 3 + 15 ng/0.3 µl/one side) and SCH23390 (DMS; 0.75 µg/0.5 µl/contralateral side); 15 min before relapse tests	6 h/d x 10 d (0.1 mg/kg/inf)	WD 1	–	Li et al., 2018a	NA
			WD 30	▼		
	Mus + Bac (AIT-L; 3 + 15 ng/0.3 µl/one side) and SCH23390 (DMS; 0.75 µg/0.5 µl/ipsilateral side); 15 min before relapse tests		WD 30	▼		
Systemic	AZD8529 (20 mg/kg, s.c.); 3 h before relapse tests	9 h/d x 10 d (0.1 mg/kg/inf)	WD 1	–	Caprioli et al., 2015	Lu et al., 2007
			WD 21	–		
	AZD8529 (40 mg/kg, s.c.); 3 h before relapse tests		WD 1	–		
			WD 21	▼		
	SYN119 (10 mg/kg, i.p.); 20 min before relapse tests	6 h/d x 10 d (0.1 mg/kg/inf)	WD1	–	Scheyer et al., 2016	Loweth et al., 2014b
			WD 44 or 52 (counterbalanced with vehicle)	▼		
	SYN119 (10 mg/kg, i.p.); WD 1 (after day 1 test), 3, 5, 7	6 h/d x 10 d (0.1 mg/kg/inf)	WD 9	–	Murray et al., 2019	
	Oxytocin (1 mg/kg, i.p.); WD 6-20	6 h/d x 10 d (0.1 mg/kg/50 µl inf)	WD 30	▼	Everett et al., 2020	NA
Food choice-induced voluntary abstinence						
NAc core	Mus+Bac (50 + 50 ng/0.5 µl/side); 15 min before relapse tests	Food: 6 h/d x 6 d, 1% sucrose + maltodextrin/ delivery Meth: 6 h/d x 12 d (0.1 mg/kg/inf)	WD 1	–	Rossi et al., 2020	NA
			WD 15	▼		
	SCH39166 (1 µg/0.5 µl/side); 15 min before relapse tests		WD 15	▼		
	Raclopride (1 µg/0.5 µl/side); 15 min before relapse tests		WD 15	▼		
	Flupenthixol (10 µg/0.5 µl/side); 15 min before relapse tests		WD 15	▼		
NAc shell	Mus+Bac (50 + 50 ng/0.5 µl/side); 15 min before relapse tests	Food: 6 h/d x 6 d, 1% sucrose + maltodextrin/ delivery Meth: 6 h/d x 12 d (0.1 mg/kg/inf)	WD 1	–	Rossi et al., 2020	NA
			WD 15	–		

(*continued on next page*)

Table 2 (*continued*)

Site of manipulation	Manipulations	SA procedure (dose)	Withdrawal day	Behavioral outcomes	Citation	Parallel incubation studies with cocaine
DMS	SCH39166 (1 μg/0.5 μl/side) ; 15 min before relapse tests	Food: 6 h/d x 6 d (5 pellets/ delivery)	WD 1	–	Caprioli et al., 2017	NA
			WD 21	▼		
	Raclopride (1 μg/0.5 μl/side); 15 min before relapse tests	Meth: 6 h/d x 12 d (0.1 mg/kg/inf)	WD 1	–		
			WD 21	▼		
	Daun02 injections (4 μg/1 μl/side); 75 min after 15-min induction sessions, 3 d before relapse tests		WD 21	▼		
Systemic	AZD8529 (20 mg/kg, s.c.); 3 h before relapse tests	Food: 9 h/d x 6 d (5 pellets/ delivery)	WD 1	–	Caprioli et al., 2015	NA
			WD 21	–		
	AZD8529 (40 mg/kg, s.c.); 3 h before relapse tests	Meth: 9 h/d x 10 d (0.1 mg/kg/inf)	WD 1	–		
			WD 21	▼		
Social choice-induced voluntary abstinence						
CeA	CeL PKCδ knockdown; AAV-shPKCδ injections before SA training	Social: 15 trials/d x 6 d	WD 1	–	Venniro et al., 2020	NA
		Meth: 6 h/d x 12 d (0.1 mg/kg/inf)	WD 15	▲		

Abbreviations: Mus: muscimol; Bac: baclofen; dmPFC: dorsomedial prefrontal cortex; vmPFC: ventromedial prefrontal cortex; OFC: orbitofrontal cortex; NAc: nucleus accumbens; DS: dorsal striatum; DMS: dorsomedial striatum; DLS: dorsolateral striatum; BLA: basolateral amygdala; CeA: central nucleus of amygdala; CeM: medial CeA; CeL: lateral CeA; AIT: anterior intralaminar nucleus of thalamus; AIT-L: lateral AIT; AIT-M: medial AIT; SA: self-administration; AAV: adeno-associated virus; SOM: somatostatin; PKC: protein kinase C; i.p.: intraperitoneal injections; s.c.: subcutaneous injections; WD: withdrawal day; inf: infusion; NA: not available. Symbols: (▲) increased Meth seeking; (▼) decreased Meth seeking; (–) no effect intake about or below 6 mg/kg/d (McFadden et al., 2012; Schwendt et al., 2009).

In the past 5 years, we also examined transcriptional regulations across multiple brain areas (Li et al., 2015d; Li et al., 2019; Cates et al., 2018) during incubation of Meth craving. In the first study (Li et al., 2015d), we reported that mRNA expressions of *Bdnf* and *TrkB,* glutamate receptors, and epigenetic enzymes in DS homogenate exhibit minimal changes on either withdrawal day 2 and 35, compared with saline rats. In contrast, we found increased mRNA expressions of several genes in Fos [the neuronal activity marker (Cruz et al., 2013)]-positive DS neurons [isolated by fluorescence activated cells sorting (FACS)] after the late withdrawal day-relapse tests (withdrawal day 30 to 50), compared with non-activated DS neurons in Meth rats. These data suggest that unique molecular alterations associated with Meth seeking occur selectively in Fos-positive neurons during prolonged withdrawal from Meth self-administration. In a follow-up study (Li et al., 2019), we examined the same genes in Fos-positive neurons in dorsomedial striatum (DMS) and anterior intralaminar nucleus of thalamus (AIT) after the day-30 relapse test in both saline and Meth rats. Unexpectedly, while we observed changes of mRNA expressions of several genes in Fos-positive neurons compared with Fos-negative neurons in both brain regions, these gene alterations are not drug-specific and also occur in rats that self-administered saline. In future studies, genome-wide analysis of these behaviorally-activated neurons may reveal drug-specific gene alterations.

Recently, we used RNA-sequencing and examined transcriptional regulations in the orbitofrontal cortex (OFC) and the central amygdala (CeA) during incubation of Meth craving (Cates et al., 2018). We reported a 10-fold increase in differentially expressed genes (DEGs) in CeA on withdrawal day 35 compared to withdrawal day 2. Additionally, upregulated DEGs on withdrawal day 35 are enriched in various biological processes, such as histone modifications and protein ubiquitination. In contrast, much fewer DEGs are identified in OFC, with more DEGs on withdrawal day 2 than withdrawal day 35. These findings are consistent with the critical role of CeA, but not OFC, in incubated Meth seeking (Li et al., 2015c) (see more details in 2.2).

Additional focuses include neurogenesis in hippocampus and glutamate-associated synaptic plasticity across striatum, medial prefrontal cortex (mPFC) and perirhinal cortex (PRH). Recinto et al. (2012) reported increased number of progenitor cells and expression of a biomarker (Ki-67) for cell proliferation in hippocampus on withdrawal day 28, implicating a potential role of neurogenesis in hippocampus in Meth relapse. Regarding glutamate-associated synaptic plasticity, Reichel et al. (2011) and Schwendt et al. (2012) reported that on withdrawal day 14, metabotropic glutamate receptor 5 (mGlu5) expression in crude membrane fraction of PRH decreases, and surface and total protein expression of mGlu2/3 in both NAc and DS decrease, accompanied with decreased surface expression of mGlu2/3 and mGlu7 in mPFC. Furthermore, mGlu2 alone exhibits no changes in either mPFC or PRH on withdrawal day 7, although changes coupled with serotonin receptors were reported in both brain regions (Hamor et al., 2018). It is of note that Schwendt et al. (2012) also demonstrated that extinction training after Meth self-administration reverses the decrease of mGlu2/3 in NAc and DS as described above, which supports the notion that dissociable neural mechanisms underlie extinction training versus abstinence after drug self-administration (Wolf, 2016; Reiner et al., 2019; Sutton et al., 2003; Knackstedt et al., 2010; Shaham and Hope, 2005).

In addition, Reichel et al. (2014) and Scofield et al. (2015) reported that PRH, on withdrawal day 7, exhibits decreased GluN2B expression in crude membrane fraction, decreased GluN2B surface expression and inability for LTD induction, an effect reversed by an NMDA receptor agonist. Furthermore, on withdrawal day 8, Mishra et al. (2017) demonstrated decreased AMPA/NMDA ratio in mPFC, possibly contributed by increased NMDA-mediated currents and increased GluN2B surface expression. In contrast, in NAc, changes occur presynaptically, with decreased paired-pulse ratio and increased frequency of spontaneous excitatory postsynaptic potential (sEPSC) (Mishra et al., 2017). These observations above, especially in PRH, have been linked to novel object memory deficits after withdrawal from Meth self-administration, and mGlu5 in PRH plays a critical role in shifting rats from seeking Meth-associated cues to novel cues during relapse tests (Peters et al., 2016).

Lastly, two studies examined sex differences after withdrawal from Meth self-administration. At the synaptic level, Pena-Bravo et al. (2019) reported that females exhibit decreased basal glutamate excitatory strength (e.g., lower amplitude of sEPSC) in prelimbic cortex (PL) between withdrawal day 9 and 14, compared with males. Furthermore, female Meth rats, but not male Meth rats, exhibit increased amplitude of evoked EPSC compared with their respective saline groups. At the transcriptional level, Daiwile et al. (2019) reported that in NAc, females have higher baseline levels of prodynorphin (*Pdyn)* mRNA than males, but on withdrawal day 30, *Pdyn* mRNA expression selectively increases in males and hypocretin receptor 2 (*Hcrtr2)* mRNA expression selectively decreases in females. It is of note that while Pena-Bravo et al. (2019) and Daiwile et al. (2019) reported no sex differences in Meth seeking, Daiwile et al. (2019) reported higher Meth intake in males than females during self-administration, which may be potentially due to different rat strains and contribute to the sex differences in transcriptional regulations.

2.2. *Role of discrete brain regions and associated neural circuits*

2.2.1. *Central amygdala (CeA)*

In a functional mapping study, we reported that CeA inactivation by a mixture of $GABA_A$ and $GABA_B$ agonists (muscimol + baclofen) decreases Meth seeking on withdrawal day 30, but not day 2, indicating a critical role of CeA in incubation of Meth craving (Li et al., 2015c). This finding is in line with earlier studies showing that inactivation of CeA activity decreases incubation of cocaine (Lu et al., 2005; Lu et al., 2007), nicotine (Funk et al., 2016) and sucrose craving (Uejima et al., 2007) assessed by the self-administration procedure, as well as incubation of morphine craving assessed by the conditioned place preference procedure (Li et al., 2008). Moreover, CeA has been identified as a common hub for incubation of cocaine, heroin and sucrose craving, based on the analyses of synaptic proteins, gene expressions and neurotransmitters related to glutamatergic, GABAergic and endocannabinoid systems across cortical, striatal and amygdalar regions (Roura-Martinez et al., 2020). Taken together, these findings implicated CeA as a common anatomical locus underlying incubation of craving to drug and non-drug reward.

Additionally, we reported that dorsomedial PFC (dmPFC), ventromedial PFC (vmPFC), OFC and basolateral amygdala (BLA) inactivation has no effect on Meth seeking on withdrawal day 30 (Li et al., 2015c). In contrast to the previous studies implicating these brain regions in incubation of cocaine (Koya et al., 2009; Lee et al., 2013; Ma et al., 2014; Shin et al., 2016; Miller et al., 2017) and opioid craving (Altshuler et al., 2020; Fanous et al., 2012), the negative findings here suggest that the role of these brain regions in incubation of craving might be drug-specific or beyond acute neuronal activity assessed by the reversible inactivation approach.

Two studies further dissected the cell-type specific role of CeA subregions (lateral vs medial division, CeL vs CeM) in incubation of Meth craving after either forced abstinence or social choice-induced voluntary abstinence (Venniro et al., 2018; Venniro et al., 2020). Here we briefly describe the main findings on the forced abstinence procedure (also see more discussion in Section 3). The authors reported that Meth seeking on withdrawal day 15 is associated with Fos induction in CeM output neurons and somatostatin (SOM)-expressing neurons in CeL (Venniro et al., 2018). Moreover, SOM knockdown in CeL, which selectively decreases Fos expression of SOM-expressing neurons, decreases Meth seeking on withdrawal day 15 (but not day 1), accompanied with decreased Fos expression in CeM output neurons (Venniro et al., 2020). Overall, these data demonstrated a critical role of SOM-expressing neurons in CeL in incubation of Meth craving after forced abstinence.

2.2.2. Dorsal striatum (DS) and associated circuits

DS is another brain region implicated in incubation of Meth craving. First, we reported that Meth seeking between withdrawal day 30 and 50 is associated with increased *Fos* mRNA of both dopamine receptor 1 (*Drd1*)- and dopamine receptor 2 (*Drd2*)-expressing neurons in DS (Li et al., 2015dd). DS Injections of SCH23390, a D1-family receptor antagonist that inhibits cue-induced Fos induction in striatum (Valjent et al., 2000), decrease Meth seeking on withdrawal day 30, but not day 2 (Li et al., 2015dd), demonstrating a critical role of D1R-mediated signaling in DS in incubation of Meth craving. Furthermore, SCH23390 injections into either DS subregion (dorsomedial or dorsolateral striatum, DMS or DLS) alone also decrease Meth seeking on withdrawal day 30 (Li et al., 2015d). This finding is in contrast to the previous studies showing dissociable roles of DMS and DLS in cue-controlled cocaine seeking (Murray et al., 2012), and context-induced reinstatement of cocaine (Bossert et al., 2009) and Meth seeking (Rubio et al., 2015).

In a follow-up circuit mapping study (Li et al., 2018a), we reported that Meth seeking on withdrawal day 30 is associated with activation of AIT (assessed by Fos) and AIT➔DMS projections (assessed by Fos and a retrograde tracer, cholera toxin B, CTb). Muscimol + baclofen injections into lateral AIT (AIT-L), but not medial AIT (AIT-M), decreases Meth seeking on withdrawal day 30. In addition, anatomical disconnections of AIT-L➔DMS, which disrupted the local interaction between glutamatergic projections (muscimol + baclofen injections into AIT-L) and postsynaptic D1R signaling (SCH23390 injections into contralateral DMS), decrease Meth seeking on withdrawal day 30, but not day 1. Our recent circuit mapping study focusing on DLS also showed that incubated Meth seeking was associated with activation of AIT➔DLS projections in female rats, suggesting that AIT➔DLS may also play a role in incubation of Meth craving (Davis et al., 2019). These results, together with recent findings showing the reinforcing effect of optogenetic activation of AIT➔DS projections in mice (Cover et al., 2019), highlight the novel role of AIT➔DS in reward seeking behavior.

2.3. Role of glutamate transmission

Caprioli et al. (2015) assessed the role of mGlu2, primarily expressed on presynaptic glutamatergic neurons (Schoepp, 2001), in incubation of Meth craving after either forced abstinence or food choice-induced voluntary abstinence. Regarding the forced abstinence model, they found that systemic injections of the novel positive allosteric modulator (PAM) of mGlu2, AZD8529, which decreases evoked glutamate release (Galici et al., 2006; Schaffhauser et al., 2003), decrease Meth seeking on withdrawal day 21, but not day 1, indicating a critical role of mGlu2 in incubation of Meth craving. This finding is in agreement with the early observation that decreased mGlu2/3 surface expression in PFC, NAc, and DS, is associated with prolonged withdrawal from Meth self-administration (Schwendt et al., 2012), and that systemic injections of LY379268 (a mGlu2/3 agonist) also decrease incubation of cocaine craving after forced abstinence (Lu et al., 2007). Moreover, systemic injections of AZD8529 decrease cue-induced reinstatement of nicotine and alcohol seeking in squirrel monkeys (Justinova et al., 2015) and rats (Augier et al., 2016), suggesting that mGlu2 plays critical roles in relapse across drug classes.

Two studies from the Wolf group focused on the role of Ca^{2+}-permeable AMPA receptors (CP-AMPARs) and mGlu1-mediated synaptic depression in NAc core in incubation of Meth craving (Scheyer et al., 2016; Murray et al., 2019), which was built on their seminal findings with cocaine over the past 12 years (Wolf, 2016; Loweth et al., 2014a; Loweth et al., 2014b; Wolf and Ferrario, 2010; Wolf and Tseng, 2012; Conrad et al., 2008). First, Scheyer et al. (2016) used whole-cell patch clamp electrophysiological recording and reported that bath-applied Naspm, a CP-AMPAR antagonist, produces a significantly greater reduction of EPSC held at −70 mv ($EPSC_{-70\ mv}$) in NAc core in Meth than saline rats on withdrawal day 7–8, an effect lasting beyond withdrawal day 40. Additionally, bath-applied SYN119, an mGlu1 PAM, decreases $EPSC_{-70\ mv}$ in NAc core of Meth rats after withdrawal day 40, with no further decrease observed after subsequent Naspm applications. Finally, authors reported that either a single intra-NAc injection of Naspm or systemic injection of SYN119 decreases incubated Meth seeking beyond withdrawal day 40. In a follow-up study, Murray et al. (2019) used biochemical methods and reported that incubation of Meth craving is accompanied with increased GluA1 translation in NAc core, but no changes in GluA1–3, mGlu1 surface and total protein expression, or coupling between mGlu1 and its scaffolding protein Homer. Moreover, authors reported that repeated systemic injections of SYN119 during early withdrawal has no effect on delaying the elevation of Meth seeking on withdrawal day 9.

Taken together, two studies above demonstrated both similarities and differences in the role of glutamate adaptations in NAc core between incubation of Meth and cocaine craving. Similar to cocaine (Loweth et al., 2014b; Conrad et al., 2008; Stefanik et al., 2018; McCutcheon et al., 2011; Scheyer et al., 2018), CP-AMPARs and mGlu1-mediated synaptic depression emerge in NAc core during incubation of Meth craving and contribute to the long-term maintenance of incubated Meth seeking; another shared neural adaptation is increased GluA1 translation, suggesting that elevated CP-AMPARs in NAc core could be contributed by accumulation of homomeric GluA1 with both drugs. Regarding differences from cocaine, there are three major ones. First, incubation of Meth craving exhibits an accelerated time-course of elevating CP-AMPARs in NAc core, which occurs as early as 7-day withdrawal, compared with 1-month withdrawal from cocaine. In parallel, Meth seeking is maximal on withdrawal day 7(Adhikary et al., 2017; Scheyer et al., 2016), while cocaine seeking starts rising on withdrawal day 7 and reaches maximum 1–2 months later (Pickens et al., 2011; Lu et al., 2004). These results suggest that elevations of CP-AMPARs in NAc core might contribute the maximal expression of incubated cocaine or Meth seeking. However, no studies have directly examined the causal role of CP-AMPARs in NAc core in cocaine or Meth seeking on withdrawal day 7. Second, unlike cocaine (Loweth et al., 2014b; Conrad et al., 2008), incubation of Meth craving is not accompanied with increased GluA1 or decreased mGlu1 surface expression that could underlie the electrophysiological manifestation of CP-AMPARs and mGlu1-mediated depression in NAc core. These results suggest that accumulation of CP-AMPARs in NAc core during incubation of Meth craving might be contributed by subtle biochemical changes that are below the sensitivity of detection. Finally, repeated systemic mGlu1 PAM blocks incubation of cocaine (Loweth et al., 2014b), but not Meth craving (Murray et al., 2019). However, it is noted that the duration of mGlu1 PAM treatment for cocaine is twice as long as for Meth, which might explain the differences between two studies.

2.4. Other mechanisms

Two studies examined additional mechanisms underlying incubation of Meth craving after forced abstinence, including the epigenetic enzyme, histone deacetylase 5 (HDAC5) and the neuropeptide, oxytocin. In the first study, we reported that viral-mediated overexpression of the nuclear-localized HDAC5 and knockdown of HDAC5 in DS increases and decreases Meth seeking on withdrawal day 30, respectively; neither manipulation affects Meth seeking on withdrawal day 2 (Li et al., 2018b). These findings together demonstrated a critical role of HDAC5 in DS in incubation of Meth craving, which are in contrast with the previous study showing that overexpression of the nuclear-localized HDAC5 in NAc decreases reinstatement of cocaine seeking after short-access cocaine self-administration training and extinction (Taniguchi et al., 2017). However, direct comparisons between cocaine and Meth study should be made with caution, because of different self-administration procedures (short-access vs long-access) and relapse models (reinstatement after extinction vs incubation of craving) used, and brain regions of interest (NAc and DS).

In the second study, Everett et al. (2020) reported that daily systemic injections of oxytocin between withdrawal day 6 and 20 decrease incubated Meth seeking on withdrawal day 30 and subsequent Meth-primed reinstatement of Meth seeking in rats of both sexes, and yohimbine-induced reinstatement of Meth seeking in female rats. Interestingly, this effect of chronic oxytocin is selective in rats with a history of extended-access, but not short-access self-administration training, which may be attributed to the role of oxytocin in offsetting the increased anxiety observed in extended-access rats. Overall, these results extend previous findings on the role of oxytocin in reinstatement of Meth seeking (Cox et al., 2017; Everett et al., 2018; Ferland et al., 2016; Baracz et al., 2016; Everett et al., 2019; Carson et al., 2010; Cox et al., 2013), and from a clinical perspective, implicates oxytocin as a potential treatment strategy to prevent Meth relapse. Finally, these results are also consistent with cocaine studies in which systemic or brain-site specific injections of oxytocin reduce reinstatement of cocaine seeking (Morales-Rivera et al., 2014; Weber et al., 2018; Leong et al., 2016; Zhou et al., 2014; Kohtz et al., 2018), suggesting a shared role of oxytocin in cocaine and Meth relapse.

2.5. *Summary*

Several studies have demonstrated neural adaptations at transcription and synaptic levels across multiple brain regions during prolonged withdrawal from extended Meth self-administration, but direct comparison should be made with caution, because of different Meth self-administration procedures used across these studies. In contrast, only a handful of studies identified neural mechanisms that play causal roles in incubation of Meth craving. These studies not only uncovered similarities (e.g., critical roles of CeA and CP-AMPARs in NAc core) and differences (e.g., roles of vmPFC and BLA) between incubation of cocaine and Meth craving, but also demonstrated novel brain circuits underlying incubation of Meth craving (e.g., AIT➔DMS projections). Finally, while all functional studies described above used male rats, it is possible that these findings do not apply to female rats, based on the observations that transcriptional and synaptic changes exhibit sex differences during withdrawal from Meth self-administration. Indeed, as described above, chronic oxytocin treatment led to selective decrease of yohimbine-induced reinstatement of Meth seeking in female rats (Everett et al., 2020).

3. Neural mechanisms underlying incubation of methamphetamine craving after choice-induced voluntary abstinence

Below we discuss five studies examining mechanisms underlying incubation of Meth craving after choice-induced voluntary abstinence, as well as similarities and differences compared with incubation of Meth craving after forced abstinence. It is important to note that while incubation of Meth craving occurs after food choice-induced voluntary abstinence (Caprioli et al., 2015), social choice-induced voluntary abstinence prevents incubation of Meth craving (Venniro et al., 2018). We summarized the causal findings from these studies in Table 2.

3.1. *Food choice-induced voluntary abstinence*

Caprioli et al. (2015) reported that systemic injections of AZD8529, an mGlu2 PAM, decrease incubated Meth seeking after forced or food choice-induced voluntary abstinence on withdrawal day 21, but not day 1, indicating a generalized role of mGlu2 in incubation of Meth craving after forced (see more discussion in Section 2.2) and choice-induced voluntary abstinence. Two additional studies focused on the role of DS and NAc in incubation of Meth craving after food choice-induced voluntary abstinence. Caprioli et al. (2017) reported that incubated Meth seeking on withdrawal day 21, but not day 1, is associated with *Fos* induction in *Drd1*- and *Drd2*-expressing cells in DMS, but not DLS. The absence of *Fos* induction in DLS, compared with the previous forced-abstinence study (Li et al., 2015d), provides the initial evidence for the dissociable mechanisms underlying incubation of Meth craving after forced versus choice-induced voluntary abstinence. Furthermore, DMS injections of SCH39166 or raclopride (D1R- and D2R-family antagonists, respectively) decrease Meth seeking on withdrawal day 21, but not day 1. Additionally, chemogenetic ablation of Fos-expressing DMS neurons activated by relapse tests in *Fos-LacZ* transgenic rats decreases Meth seeking on withdrawal day 21. Together with our previous study (Li et al., 2015d), these findings indicate that DMS plays a generalized role in incubation of Meth craving after forced abstinence and food choice-induced voluntary abstinence.

In a subsequent study, Rossi et al. (2020) reported that incubated Meth seeking on withdrawal day 15, but not day 1, is associated with *Fos* induction in *Drd1*- and *Drd2*-expressing cells in NAc core, but not NAc shell. Furthermore, NAc core, but not shell, injections of muscimol + baclofen decrease Meth seeking on withdrawal day 15, but not day 1. NAc core injections of SCH39166 or raclopride also decrease Meth seeking on withdrawal day 15. Taken together with the previous study demonstrating a critical role of CP-AMPARs in NAc core in incubation of Meth craving after forced abstinence (Scheyer et al., 2016), these results suggest a generalized role of NAc core in incubation of Meth craving after either forced or choice-induced voluntary abstinence.

3.2. *Social choice-induced voluntary abstinence*

Two studies focused on CeA, previously implicated in both incubation of Meth craving after forced abstinence (Li et al., 2015c) and Meth relapse after food choice-induced voluntary abstinence (Venniro et al., 2017), and explored neural mechanisms underlying the suppressing effect of social choice-induced voluntary abstinence on incubation of Meth craving. First, Venniro et al. (2018) reported that on withdrawal day 15, while Meth seeking after forced abstinence is associated with *Fos* induction in CeM and SOM-expressing neurons in CeL, Meth seeking after social choice-induced voluntary abstinence is only associated Fos induction in protein kinase C δ (PKCδ)-expressing neurons in CeL. In a follow-up study, Venniro et al. (2020) demonstrated that SOM-expressing neurons in CeL plays a critical role in incubation of Meth craving after forced abstinence (see more details in Section 2.2). In contrast, PKCδ knockdown in CeL, which decreases neuronal activation of PKCδ-expressing neurons, increases Meth seeking on withdrawal day 15 (but not day 1) after social choice-induced voluntary abstinence, accompanied with increased Fos induction in CeM. These results indicated that PKCδ-expressing neurons in CeL, through inhibiting neuronal activation of CeM output neurons, play a critical role in the inhibitory effect of social choice-induced voluntary abstinence on incubation of Meth craving. Together, these findings provide the initial evidence at the function level for abstinence-dependent neural mechanisms underlying incubation of Meth craving.

4. Neural mechanisms underlying incubation of Meth craving after punishment-induced abstinence

So far only three correlations studies examined the molecular adaptions and circuit activities associated with incubation of Meth craving after punishment-induced abstinence. Below we discuss the main findings from these studies and further details are summarized in Table 1. At the molecular level, Krasnova et al. (2017) reported mRNA levels of oxytocin in NAc and cocaine-and-amphetamine-regulated transcript (CART) prepropeptide (*CARTpt)* in DS selectively increase in shock-resistant rats 30 days after the last punishment session. Authors also observed changes of additional genes (e.g., oxytocin receptors, metabolic enzymes) in NAc and DS, but these changes are either similar or relative to yoked-shock control rats, indicating an effect of shock alone. Later, Torres et al. (2018) focused on neurotrophins and associated mitogen-activated protein kinase (MAPK) signaling in DS and reported increased mRNA expression of several neurotrophins, including *Bdnf*, in shock-sensitive rats, compared with shock-resistant rats, 30 days after the last punishment session. In both shock-sensitive and shock-resistant rats, BDNF protein level increases in DS, while increases of tyrosine kinase A phosphorylation and several phosphorylated proteins associated with MAPK are only observed in short-sensitive rats. However, no shock control rats were used in this study and therefore it is unclear whether these effects are associated with shock or not.

At the circuity level, Hu et al. (2019) used fMRI and identified neural circuits associated with Meth self-administration and punishment-induced abstinence. Authors reported an increase in circuit strength of OFC➔DMS projections and a decrease in circuit strength of prelimbic cortex (PrL)➔ventrolateral striatum (VLS) projections after 20-d Meth self-administration. Shock-resistant rats exhibit strengthening of the negative connectivity after 5-d punishment sessions, while circuit strength of PrL➔VLS returns to baseline. Interestingly, circuitry strength in all rats returns to baseline after 30-day withdrawal from the last punishment session, suggesting that these changes might not be implicated in incubation process after punishment-induced abstinence.

5. Conclusion and future directions

In the past five years, a growing body of studies started examining causal roles of neural mechanisms underlying incubation of Meth craving, which extended studies focusing on correlations between neural adaptation and prolonged withdrawal from extended-access Meth self-administration. The majority of these causal studies used forced abstinence procedures. Furthermore, these causal studies identified either parallel or distinct mechanisms between incubation of Meth and cocaine craving (see Table 2). Together with evidence demonstrating distinct neural mechanisms between incubation of craving to opioid and psychostimulants (Li et al., 2015c; Altshuler et al., 2020; Fanous et al., 2012), these findings indicated that neural mechanisms underlying incubation of drug craving differ not only across drug classes, but also within drug classes.

A handful of studies examined causal neural mechanisms underlying incubation of Meth craving after choice-induced voluntary abstinence. Compared with studies using forced abstinence procedure, these studies also identified neural mechanisms that are either abstinence-independent or abstinence-dependent. Especially the new study from Venniro et al. (2020) highlighted differences in cell-type specific microcircuitry within the CeA that plays critical roles in incubation of Meth craving after forced abstinence as opposed to social choice-induced abstinence. In contrast, studies focusing on punishment-induced abstinence have all been association studies. Furthermore, it is difficult to disentangle neuroadaptations using the punishment procedure as the shock alone leads to molecular changes (see details in Section 4).

Together, these causal studies provided potential therapeutic targets (e.g., CP-AMPARs, oxytocin) for future clinical studies to develop effective treatment for preventing Meth relapse and to further our understanding of the neurological process of Meth users who undergo voluntary abstinence. These studies also raised additional key questions for future preclinical studies: what contributes to the distinct neural mechanisms underlying incubation of cocaine versus Meth craving after forced abstinence? What neural mechanisms play a casual role in incubation of Meth craving after punishment-induced abstinence? Finally, correlational studies identified sex differences in neural substrates during incubation of Meth craving and it would be important to examine whether these substrates play causal roles at the behavioral level.

CRediT authorship contribution statement

RDA, HL and XL wrote the manuscript.

Declaration of competing interest

The authors declare that they do not have any conflicts of interest (financial or otherwise) related to the text of the paper. The write-up of the review was supported by NARSAD Young Investigator Award (XL) and NIH/NIDA R00DA041350-02 (XL) and departmental startup funds (XL).

References

Abdolahi, A., Acosta, G., Breslin, F.J., Hemby, S.E., Lynch, W.J., 2010. Incubation of nicotine seeking is associated with enhanced protein kinase A-regulated signaling of dopamine- and cAMP-regulated phosphoprotein of 32 kDa in the insular cortex. Eur. J. Neurosci. 31 (4), 733–741.

Adhikary, S., Caprioli, D., Venniro, M., Kallenberger, P., Shaham, Y., Bossert, J.M., 2017. Incubation of extinction responding and cue-induced reinstatement, but not context- or drug priming-induced reinstatement, after withdrawal from methamphetamine. Addict. Biol. 22 (4), 977–990.

Altshuler, R.D., Yang, E.S., Garcia, K.T., et al., 2020. Role of orbitofrontal cortex in incubation of oxycodone craving in male rats. Addict. Biol. e12927.

Augier, E., Dulman, R.S., Rauffenbart, C., Augier, G., Cross, A.J., Heilig, M., 2016. The mGluR2 positive allosteric modulator, AZD8529, and cue-induced relapse to alcohol seeking in rats. Neuropsychopharmacology 41 (12), 2932–2940.

Baracz, S.J., Everett, N.A., McGregor, I.S., Cornish, J.L., 2016. Oxytocin in the nucleus accumbens core reduces reinstatement of methamphetamine-seeking behaviour in rats. Addict. Biol. 21 (2), 316–325.

Bedi, G., Preston, K.L., Epstein, D.H., et al., 2011. Incubation of cue-induced cigarette craving during abstinence in human smokers. Biol. Psychiatry 69 (7), 708–711.

Bienkowski, P., Rogowski, A., Korkosz, A., et al., 2004. Time-dependent changes in alcohol-seeking behaviour during abstinence. Eur. Neuropsychopharmacol. 14 (5), 355–360.

Bossert, J.M., Wihbey, K.A., Pickens, C.L., Nair, S.G., Shaham, Y., 2009. Role of dopamine D(1)-family receptors in dorsolateral striatum in context-induced reinstatement of heroin seeking in rats. Psychopharmacology 206 (1), 51–60.

Brecht, M.L., Herbeck, D., 2014. Time to relapse following treatment for methamphetamine use: a long-term perspective on patterns and predictors. Drug Alcohol Depend. 139, 18–25.

Burman, S., 1997. The challenge of sobriety: natural recovery without treatment and self-help groups. J. Subst. Abus. 9, 41–61.

Caprioli, D., Venniro, M., Zeric, T., et al., 2015. Effect of the novel positive allosteric modulator of metabotropic glutamate receptor 2 AZD8529 on incubation of methamphetamine craving after prolonged voluntary abstinence in a rat model. Biol. Psychiatry 78 (7), 463–473.

Caprioli, D., Venniro, M., Zhang, M., et al., 2017. Role of dorsomedial striatum neuronal ensembles in incubation of methamphetamine craving after voluntary abstinence. J. Neurosci. 37 (4), 1014–1027.

Carson, D.S., Cornish, J.L., Guastella, A.J., Hunt, G.E., McGregor, I.S., 2010. Oxytocin decreases methamphetamine self-administration, methamphetamine hyperactivity, and relapse to methamphetamine-seeking behaviour in rats. Neuropharmacology 58 (1), 38–43.

Cates, H.M., Li, X., Purushothaman, I., et al., 2018. Genome-wide transcriptional profiling of central amygdala and orbitofrontal cortex during incubation of methamphetamine craving. Neuropsychopharmacology 43 (12), 2426–2434.

Conrad, K.L., Tseng, K.Y., Uejima, J.L., et al., 2008. Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of cocaine craving. Nature 454 (7200), 118–121.

Cover, K.K., Gyawali, U., Kerkhoff, W.G., et al., 2019. Activation of the rostral intralaminar thalamus drives reinforcement through striatal dopamine release. Cell Rep. 26, 1389–1398.

Cox, B.M., Young, A.B., See, R.E., Reichel, C.M., 2013. Sex differences in methamphetamine seeking in rats: impact of oxytocin. Psychoneuroendocrinology 38 (10), 2343–2353.

Cox, B.M., Bentzley, B.S., Regen-Tuero, H., See, R.E., Reichel, C.M., Aston-Jones, G., 2017. Oxytocin acts in nucleus accumbens to attenuate methamphetamine seeking and demand. Biol. Psychiatry 81 (11), 949–958.

Cruz, F.C., Koya, E., Guez-Barber, D.H., et al., 2013. New technologies for examining the role of neuronal ensembles in drug addiction and fear. Nat. Rev. Neurosci. 14 (11), 743–754.

Daiwile, A.P., Jayanthi, S., Ladenheim, B., et al., 2019. Sex differences in escalated methamphetamine self-administration and altered gene expression associated with incubation of methamphetamine seeking. Int. J. Neuropsychopharmacol. 22 (11), 710–723.

D'Arcy, C., Luevano, J.E., Miranda-Arango, M., et al., 2016. Extended access to methamphetamine self-administration up-regulates dopamine transporter levels 72 hours after withdrawal in rats. Behav. Brain Res. 296, 125–128.

Davis, I.R., Coldren, S.S., Li, X., 2019. Role of afferent projections to dorsolateral striatum in incubation of methamphetamine craving in male and female rats. In: Paper

Presented at: Society for Neuroscience Annual Meeting 2019, (Chicago, IL).

Douglass, J., McKinzie, A.A., Couceyro, P., 1995. PCR differential display identifies a rat brain mRNA that is transcriptionally regulated by cocaine and amphetamine. J. Neurosci. 15 (3), 2471.

Epstein, D.H., Preston, K.L., 2003. The reinstatement model and relapse prevention: a clinical perspective. Psychopharmacology 168 (1–2), 31–41.

Everett, N.A., McGregor, I.S., Baracz, S.J., Cornish, J.L., 2018. The role of the vasopressin V1A receptor in oxytocin modulation of methamphetamine primed reinstatement. Neuropharmacology. 133, 1–11.

Everett, N.A., Baracz, S., Cornish, J., 2019. Oxytocin treatment in the prelimbic cortex reduces relapse to methamphetamine-seeking and is associated with reduced activity in the rostral nucleus accumbens core. Pharmacol. Biochem. Behav. 183, 64–71.

Everett, N.A., Baracz, S.J., Cornish, J.L., 2020. The effect of chronic oxytocin treatment during abstinence from methamphetamine self-administration on incubation of craving, reinstatement, and anxiety. Neuropsychopharmacology 45 (4), 597–605.

Fanous, S., Goldart, E.M., Theberge, F.R., Bossert, J.M., Shaham, Y., Hope, B.T., 2012. Role of orbitofrontal cortex neuronal ensembles in the expression of incubation of heroin craving. J. Neurosci. 32 (34), 11600–11609.

Ferland, C.L., Reichel, C.M., McGinty, J.F., 2016. Effects of oxytocin on methamphetamine-seeking exacerbated by predator odor pre-exposure in rats. Psychopharmacology 233 (6), 1015–1024.

Funk, D., Coen, K., Tamadon, S., Hope, B.T., Shaham, Y., Le, A.D., 2016. Role of central amygdala neuronal ensembles in incubation of nicotine craving. J. Neurosci. 36 (33), 8612–8623.

Galici, R., Jones, C.K., Hemstapat, K., et al., 2006. Biphenyl-indanone A, a positive allosteric modulator of the metabotropic glutamate receptor subtype 2, has antipsychotic- and anxiolytic-like effects in mice. J. Pharmacol. Exp. Ther. 318 (1), 173–185.

Gawin, F.H., Kleber, H.D., 1986. Abstinence symptomatology and psychiatric diagnosis in cocaine abusers. Clinical observations. Arch. Gen. Psychiatry 43 (2), 107–113.

Grimm, J.W., Hope, B.T., Wise, R.A., Shaham, Y., 2001. Incubation of cocaine craving after withdrawal. Nature 412, 141–142.

Grimm, J.W., Fyall, A.M., Osincup, D.P., 2005. Incubation of sucrose craving: effects of reduced training and sucrose pre-loading. Physiol. Behav. 84 (1), 73–79.

Hamor, P.U., Sirova, J., Palenicek, T., Zaniewska, M., Bubenikova-Valesova, V., Schwendt, M., 2018. Chronic methamphetamine self-administration dysregulates 5-HT2A and mGlu2 receptor expression in the rat prefrontal and perirhinal cortex: comparison to chronic phencyclidine and MK-801. Pharmacol. Biochem. Behav. 175, 89–100.

Hu, Y., Salmeron, B.J., Krasnova, I.N., et al., 2019. Compulsive drug use is associated with imbalance of orbitofrontal- and prelimbic-striatal circuits in punishment-resistant individuals. Proc. Natl. Acad. Sci. U. S. A. 116 (18), 9066–9071.

Hunt, W.A., Barnett, L.W., Branch, L.G., 1971. Relapse rates in addiction programs. J. Clin. Psychol. 27 (4), 455–456.

Justinova, Z., Panlilio, L.V., Secci, M.E., et al., 2015. The novel metabotropic glutamate receptor 2 positive allosteric modulator, AZD8529, decreases nicotine self-administration and relapse in squirrel monkeys. Biol. Psychiatry 78 (7), 452–462.

Katz, J.L., Higgins, S.T., 2003. The validity of the reinstatement model of craving and relapse to drug use. Psychopharmacology 168 (1–2), 21–30.

Klingemann, H.K., 1991. The motivation for change from problem alcohol and heroin use. Br. J. Addict. 86 (6), 727–744.

Knackstedt, L.A., Moussawi, K., Lalumiere, R., Schwendt, M., Klugmann, M., Kalivas, P.W., 2010. Extinction training after cocaine self-administration induces glutamatergic plasticity to inhibit cocaine seeking. J. Neurosci. 30 (23), 7984–7992.

Kohtz, A.S., Lin, B., Smith, M.E., Aston-Jones, G., 2018. Attenuated cocaine-seeking after oxytocin administration in male and female rats. Psychopharmacology 235 (7), 2051–2063.

Koya, E., Uejima, J.L., Wihbey, K.A., Bossert, J.M., Hope, B.T., Shaham, Y., 2009. Role of ventral medial prefrontal cortex in incubation of cocaine craving. Neuropharmacology. 56 (Suppl. 1), 177–185.

Krasnova, I.N., Justinova, Z., Ladenheim, B., et al., 2010. Methamphetamine self-administration is associated with persistent biochemical alterations in striatal and cortical dopaminergic terminals in the rat. PLoS One 5 (1), e8790.

Krasnova, I.N., Chiflikyan, M., Justinova, Z., et al., 2013. CREB phosphorylation regulates striatal transcriptional responses in the self-administration model of methamphetamine addiction in the rat. Neurobiol. Dis. 58, 132–143.

Krasnova, I.N., Marchant, N.J., Ladenheim, B., et al., 2014. Incubation of methamphetamine and palatable food craving after punishment-induced abstinence. Neuropsychopharmacology 39 (8), 2008–2016.

Krasnova, I.N., Gerra, M.C., Walther, D., et al., 2017. Compulsive methamphetamine taking in the presence of punishment is associated with increased oxytocin expression in the nucleus accumbens of rats. Sci. Rep. 7 (8331), 1–14.

Kuhar, M.J., Jaworski, J.N., Hubert, G.W., Philpot, K.B., Dominguez, G., 2005. Cocaine- and amphetamine-regulated transcript peptides play a role in drug abuse and are potential therapeutic targets. AAPS J. 7 (1), E259–E265.

Lee, B.R., Ma, Y.Y., Huang, Y.H., et al., 2013. Maturation of silent synapses in amygdala-accumbens projection contributes to incubation of cocaine craving. Nat. Neurosci. 16 (11), 1644–1651.

Leong, K.C., Zhou, L., Ghee, S.M., See, R.E., Reichel, C.M., 2016. Oxytocin decreases cocaine taking, cocaine seeking, and locomotor activity in female rats. Exp. Clin. Psychopharmacol. 24 (1), 55–64.

Li, P., Wu, P., Xin, X., et al., 2015a. Incubation of alcohol craving during abstinence in patients with alcohol dependence. Addict. Biol. 20 (3), 513–522.

Li, X., Caprioli, D., Marchant, N.J., 2015b. Recent updates on incubation of drug craving: a mini-review. Addict. Biol. 20, 872–876.

Li, X., Zeric, T., Kambhampati, S., Bossert, J.M., Shaham, Y., 2015c. The central amygdala nucleus is critical for incubation of methamphetamine craving. Neuropsychopharmacology 40, 1297–1306.

Li, X., Rubio, F.J., Zeric, T., et al., 2015d. Incubation of methamphetamine craving is associated with selective increases in expression of Bdnf and trkb, glutamate receptors, and epigenetic enzymes in cue-activated fos-expressing dorsal striatal neurons. J. Neurosci. 35 (21), 8232–8244.

Li, X., Witonsky, K.R., Lofaro, O.M., et al., 2018a. Role of anterior intralaminar nuclei of thalamus projections to dorsomedial striatum in incubation of methamphetamine craving. J. Neurosci. 38 (9), 2270–2282.

Li, X., Carreria, M.B., Witonsky, K.R., et al., 2018b. Role of dorsal striatum histone deacetylase 5 in incubation of methamphetamine craving. Biol. Psychiatry 84, 213–222.

Li, X., Davis, I.R., Lofaro, O.M., Zhang, J., Cimbro, R., Rubio, F.J., 2019. Distinct gene alterations between Fos-expressing striatal and thalamic neurons after withdrawal from methamphetamine self-administration. Brain Behav 9 (9), e01378.

Li, Y.Q., Li, F.Q., Wang, X.Y., et al., 2008. Central amygdala extracellular signal-regulated kinase signaling pathway is critical to incubation of opiate craving. J. Neurosci. 28 (49), 13248–13257.

Loweth, J.A., Tseng, K.Y., Wolf, M.E., 2014a. Adaptations in AMPA receptor transmission in the nucleus accumbens contributing to incubation of cocaine craving. Neuropharmacology 76 (Pt B), 287–300.

Loweth, J.A., Scheyer, A.F., Milovanovic, M., et al., 2014b. Synaptic depression via mGluR1 positive allosteric modulation suppresses cue-induced cocaine craving. Nat. Neurosci. 17 (1), 73–80.

Lu, L., Grimm, J.W., Hope, B.T., Shaham, Y., 2004. Incubation of cocaine craving after withdrawal: a review of preclinical data. Neuropharmacology. 47 (Suppl. 1), 214–226.

Lu, L., Hope, B.T., Dempsey, J., Liu, S.Y., Bossert, J.M., Shaham, Y., 2005. Central amygdala ERK signaling pathway is critical to incubation of cocaine craving. Nat. Neurosci. 8 (2), 212–219.

Lu, L., Uejima, J.L., Gray, S.M., Bossert, J.M., Shaham, Y., 2007. Systemic and central amygdala injections of the mGluR(2/3) agonist LY379268 attenuate the expression of incubation of cocaine craving. Biol. Psychiatry 61 (5), 591–598.

Ma, Y.-Y., Lee, B.R., Wang, X., et al., 2014. Bidirectional modulation of incubation of cocaine craving by silent synapse-based remodeling of prefrontal cortex to accumbens projections. Neuron 83 (6), 1453–1467.

McCutcheon, J.E., Loweth, J.A., Ford, K.A., Marinelli, M., Wolf, M.E., Tseng, K.Y., 2011. Group I mGluR activation reverses cocaine-induced accumulation of calcium-permeable AMPA receptors in nucleus accumbens synapses via a protein kinase C-dependent mechanism. J Neurosci 31, 14536–14541.

McFadden, L.M., Hadlock, G.C., Allen, S.C., et al., 2012. Methamphetamine self-administration causes persistent striatal dopaminergic alterations and mitigates the deficits caused by a subsequent methamphetamine exposure. J. Pharmacol. Exp. Ther. 340 (2), 295–303.

Miller, B.W., Wroten, M.G., Sacramento, A.D., et al., 2017. Cocaine craving during protracted withdrawal requires PKCε priming within vmPFC. Addict. Biol. 22 (3), 629–639.

Mishra, D., Pena-Bravo, J.I., Leong, K.C., Lavin, A., Reichel, C.M., 2017. Methamphetamine self-administration modulates glutamate neurophysiology. Brain Struct. Funct. 222 (5), 2031–2039.

Morales-Rivera, A., Hernandez-Burgos, M.M., Martinez-Rivera, A., et al., 2014. Anxiolytic effects of oxytocin in cue-induced cocaine seeking behavior in rats. Psychopharmacology 231 (21), 4145–4155.

Morley, K.C., Cornish, J.L., Faingold, A., Wood, K., Haber, P.S., 2017. Pharmacotherapeutic agents in the treatment of methamphetamine dependence. Expert Opin. Investig. Drugs 26 (5), 563–578.

Murray, C.H., Loweth, J.A., Milovanovic, M., et al., 2019. AMPA receptor and metabotropic glutamate receptor 1 adaptations in the nucleus accumbens core during incubation of methamphetamine craving. Neuropsychopharmacology 44 (9), 1534–1541.

Murray, J.E., Belin, D., Everitt, B.J., 2012. Double dissociation of the dorsomedial and dorsolateral striatal control over the acquisition and performance of cocaine seeking. Neuropsychopharmacology 37 (11), 2456–2466.

O'Brien, C.P., Childress, A.R., McLellan, A.T., Ehrman, R., 1992. Classical conditioning in drug-dependent humans. Ann. N. Y. Acad. Sci. 654, 400–415.

Parvaz, M.A., Moeller, S.J., Goldstein, R.Z., 2016. Incubation of cue-induced craving in adults addicted to cocaine measured by electroencephalography. JAMA Psychiatry 73 (11), 1127–1134.

Pena-Bravo, J.I., Penrod, R., Reichel, C.M., Lavin, A., 2019. Methamphetamine self-administration elicits sex-related changes in postsynaptic glutamate transmission in the prefrontal cortex. eNeuro 6 (1).

Peters, J., Scofield, M.D., Ghee, S.M., Heinsbroek, J.A., Reichel, C.M., 2016. Perirhinal cortex mGlu5 receptor activation reduces relapse to methamphetamine seeking by restoring novelty salience. Neuropsychopharmacology 41 (6), 1477–1485.

Pickens, C.L., Airavaara, M., Theberge, F.R., Fanous, S., Hope, B., Shaham, Y., 2011. Neurobiology of incubation of cocaine craving. Trends Neurosci. 34 (8), 411–420.

Recinto, P., Samant, A.R.H., Chavez, G., et al., 2012. Levels of neural progenitors in the hippocampus predict memory impairment and relapse to drug seeking as a function of excessive methamphetamine self-administration. Neuropsychopharmacology 37 (5), 1275–1287.

Reichel, C.M., Bevins, R.A., 2009. Forced abstinence model of relapse to study pharmacological treatments of substance use disorder. Curr Drug Abuse Rev 2 (2), 184–194.

Reichel, C.M., Schwendt, M., McGinty, J.F., Olive, M.F., See, R.E., 2011. Loss of object recognition memory produced by extended access to methamphetamine self-administration is reversed by positive allosteric modulation of metabotropic glutamate receptor 5. Neuropsychopharmacology 36 (4), 782–792.

Reichel, C.M., Gilstrap, M.G., Ramsey, L.A., See, R.E., 2014. Modafinil restores methamphetamine induced object-in-place memory deficits in rats independent of glutamate N-methyl-D-aspartate receptor expression. Drug Alcohol Depend. 134, 115–122.

Reiner, D.J., Fredriksson, I., Lofaro, O.M., Bossert, J.M., Shaham, Y., 2019. Relapse to opioid seeking in rat models: behavior, pharmacology and circuits. Neuropsychopharmacology 44 (3), 465–477.

Roll, J.M., 2007. Contingency management: an evidence-based component of methamphetamine use disorder treatments. Addiction. 102 (Suppl. 1), 114–120.

Rossi, L.M., Reverte, I., Ragozzino, D., Badiani, A., Venniro, M., Caprioli, D., 2020. Role of nucleus accumbens core but not shell in incubation of methamphetamine craving after voluntary abstinence. Neuropsychopharmacology 45 (2), 256–265.

Roura-Martinez, D., Ucha, M., Orihuel, J., et al., 2020. Central nucleus of the amygdala as a common substrate of the incubation of drug and natural reinforcer seeking. Addict. Biol. 25, e12706.

Rubio, F.J., Liu, Q.R., Li, X., et al., 2015. Context-induced reinstatement of methamphetamine seeking is associated with unique molecular alterations in Fos-expressing dorsolateral striatum neurons. J. Neurosci. 35 (14), 5625–5639.

Schaffhauser, H., Rowe, B.A., Morales, S., et al., 2003. Pharmacological characterization and identification of amino acids involved in the positive modulation of metabotropic glutamate receptor subtype 2. Mol. Pharmacol. 64 (4), 798–810.

Scheyer, A.F., Christian, D.T., Wolf, M.E., Tseng, K.Y., 2018. Emergence of endocytosisdependent mGlu1 LTD at nucleus accumbens synapses after withdrawal from cocaine self-administration. Front Synaptic Neurosci 10, 36.

Scheyer, A.F., Loweth, J.A., Christian, D.T., et al., 2016. AMPA receptor plasticity in accumbens core contributes to incubation of methamphetamine craving. Biol. Psychiatry 80 (9), 661–670.

Schoepp, D.D., 2001. Unveiling the functions of presynaptic metabotropic glutamate receptors in the central nervous system. J. Pharmacol. Exp. Ther. 299 (1), 12–20.

Schwendt, M., Rocha, A., See, R.E., Pacchioni, A.M., McGinty, J.F., Kalivas, P.W., 2009. Extended methamphetamine self-administration in rats results in a selective reduction of dopamine transporter levels in the prefrontal cortex and dorsal striatum not accompanied by marked monoaminergic depletion. J. Pharmacol. Exp. Ther. 331 (2), 555–562.

Schwendt, M., Reichel, C.M., See, R.E., 2012. Extinction-dependent alterations in corticostriatal mGluR2/3 and mGluR7 receptors following chronic methamphetamine self-administration in rats. PLoS One 7 (3), e34299.

Scofield, M.D., Trantham-Davidson, H., Schwendt, M., et al., 2015. Failure to recognize novelty after extended methamphetamine self-administration results from loss of long-term depression in the perirhinal cortex. Neuropsychopharmacology 40 (11), 2526–2535.

Shaham, Y., Hope, B.T., 2005. The role of neuroadaptations in relapse to drug seeking. Nat. Neurosci. 8 (11), 1437–1439.

Shalev, U., Morales, M., Hope, B., Yap, J., Shaham, Y., 2001. Time-dependent changes in extinction behavior and stress-induced reinstatement of drug seeking following withdrawal from heroin in rats. Psychopharmacology 156 (1), 98–107.

Shepard, J.D., Bossert, J.M., Liu, S.Y., Shaham, Y., 2004. The anxiogenic drug yohimbine reinstates methamphetamine seeking in a rat model of drug relapse. Biol. Psychiatry 55 (11), 1082–1089.

Shepard, J.D., Chuang, D.T., Shaham, Y., Morales, M., 2006. Effect of methamphetamine self-administration on tyrosine hydroxylase and dopamine transporter levels in mesolimbic and nigrostriatal dopamine pathways of the rat. Psychopharmacology 185 (4), 505–513.

Shin, C.B., Serchia, M.M., Shahin, J.R., Ruppert-Majer, M.A., Kippin, T.E., Szumlinski, K.K., 2016. Incubation of cocaine-craving relates to glutamate over-flow within ventromedial prefrontal cortex. Neuropharmacology 102, 103–110.

Silverman, K., DeFulio, A., Sigurdsson, S.O., 2012. Maintenance of reinforcement to address the chronic nature of drug addiction. Prev. Med. 55 (Suppl), S46–S53.

Sinha, R., S, Y., Heilig, M., 2011. Translational and reverse translational research on the role of stress in drug craving and relapse. Psychopharamacology 218, 69–82.

Stefanik, M.T., Milovanovic, M., Werner, C.T., Spainhour, J.C.G., Wolf, M.E., 2018. Withdrawal from cocaine self-administration alters the regulation of protein translation in the nucleus accumbens. Biol. Psychiatry 84 (3), 223–232.

Sutton, M.A., Schmidt, E.F., Choi, K.H., et al., 2003. Extinction-induced upregulation in AMPA receptors reduces cocaine-seeking behaviour. Nature 421 (6918), 70–75.

Taniguchi, M., Carreira, M.B., Cooper, Y.A., et al., 2017. HDAC5 and its target gene, Npas4, function in the nucleus accumbens to regulate cocaine-conditioned behaviors. Neuron. 96 (1), 130–144 (e136).

Theberge, F.R., Li, X., Kambhampati, S., et al., 2013. Effect of chronic delivery of the Toll-like receptor 4 antagonist (+)-naltrexone on incubation of heroin craving. Biol. Psychiatry 73 (8), 729–737.

Torres, O.V., Jayanthi, S., McCoy, M.T., Cadet, J.L., 2018. Selective activation of striatal NGF-TrkA/p75NTR/MAPK intracellular signaling in rats that show suppression of methamphetamine intake 30 days following drug abstinence. Int. J. Neuropsychopharmacol. 21 (3), 281–290.

Treloar Padovano, H., Miranda Jr., R., 2020. Incubation of alcohol craving as it naturally occurs in a developmentally diverse sample of dependent and nondependent drinkers. Addict. Biol. e12934 n/a;n/a.

Uejima, J.L., Bossert, J.M., Poles, G.C., Lu, L., 2007. Systemic and central amygdala injections of the mGluR2/3 agonist LY379268 attenuate the expression of incubation of sucrose craving in rats. Behav. Brain Res. 181 (2), 292–296.

Valjent, E., Corvol, J.C., Pages, C., Besson, M.J., Maldonado, R., Caboche, J., 2000. Involvement of the extracellular signal-regulated kinase cascade for cocaine-rewarding properties. J. Neurosci. 20 (23), 8701–8709.

Venniro, M., Caprioli, D., Zhang, M., et al., 2017. The anterior insular cortex– > central amygdala glutamatergic pathway is critical to relapse after contingency management. Neuron. 96 (2), 414–427 (e418).

Venniro, M., Zhang, M., Caprioli, D., et al., 2018. Volitional social interaction prevents drug addiction in rat models. Nat. Neurosci. 21 (11), 1520–1529.

Venniro, M., Russell, T.I., Ramsey, L.A., et al., 2020. Abstinence-dependent dissociable central amygdala microcircuits control drug craving. Proc. Natl. Acad. Sci. U. S. A. 117 (14), 8126–8134.

Wang, G., Shi, J., Chen, N., et al., 2013. Effects of length of abstinence on decision-making and craving in methamphetamine abusers. PLoS One 8 (7), e68791.

Weber, R.A., Logan, C.N., Leong, K.C., Peris, J., Knackstedt, L., Reichel, C.M., 2018. Regionally specific effects of oxytocin on reinstatement of cocaine seeking in male and female rats. Int. J. Neuropsychopharmacol. 21 (7), 677–686.

Wolf, M.E., 2016. Synaptic mechanisms underlying persistent cocaine craving. Nat. Rev. Neurosci. 17 (6), 351–365.

Wolf, M.E., Ferrario, C.R., 2010. AMPA receptor plasticity in the nucleus accumbens after repeated exposure to cocaine. Neurosci. Biobehav. Rev. 35 (2), 185–211.

Wolf, M.E., Tseng, K.Y., 2012. Calcium-permeable AMPA receptors in the VTA and nucleus accumbens after cocaine exposure: when, how, and why? Front. Mol. Neurosci. 5 (72), 1–27.

Zhou, L., Sun, W.L., Young, A.B., Lee, K., McGinty, J.F., See, R.E., 2014. Oxytocin reduces cocaine seeking and reverses chronic cocaine-induced changes in glutamate receptor function. Int. J. Neuropsychopharmacol. 18 (1).