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REVIEW

Glutamate Receptors in Extinction and Extinction-Based Therapies for Psychiatric Illness

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Some psychiatric illnesses involve a learned component. For example, in posttraumatic stress disorder, memories triggered by trauma-associated cues trigger fear and anxiety, and in addiction, drug-associated cues elicit drug craving and withdrawal. Clinical interventions to reduce the impact of conditioned cues in eliciting these maladaptive conditioned responses are likely to be beneficial. Extinction is a method of lessening conditioned responses and involves repeated exposures to a cue in the absence of the event it once predicted. We believe that an improved understanding of the behavioral and neurobiological mechanisms of extinction will allow extinction-like procedures in the clinic to become more effective. Research on the role of glutamate—the major excitatory neurotransmitter in the mammalian brain—in extinction has led to the development of pharmacotherapeutics to enhance the efficacy of extinction-based protocols in clinical populations. In this review, we describe what has been learned about glutamate actions at its three major receptor types (*N*-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and metabotropic glutamate receptors) in the extinction of conditioned fear, drug craving, and withdrawal. We then discuss how these findings have been applied in clinical research.
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INTRODUCTION

Psychiatric illnesses are caused by an interaction between genetic and environmental factors. For example, post-traumatic stress disorder (PTSD) develops in vulnerable people on the basis of genetics, early life stress, and exposure to a traumatic event, and involves a constellation of symptoms, including intrusive memories and re-experiencing of the trauma ('flashbacks') (American Psychiatric Association, 2000). It is believed that these symptoms arise in part through a Pavlovian conditioning process in which cues present at the time of trauma acquire the ability to elicit fear. Over time, generalization from those cues to other cues and situations leads to pervasive, inappropriate fear and anxiety (Rothbaum and Davis, 2003). Addiction also involves a Pavlovian conditioning component in that cues that reliably precede the onset of drug effects, such as drug paraphernalia, acquire the ability to trigger powerful drug craving and withdrawal responses that contribute to the maintenance of and relapse to drug use (Childress *et al*, 1986).

There has been considerable interest in developing clinical interventions to reduce the impact of conditioned cues in eliciting these maladaptive responses. One method by which Pavlovian-conditioned responses can be lessened is extinction, a protocol involving repeated or prolonged exposure to a cue (known as the conditioned stimulus) in the absence of the event it once predicted (known as the unconditioned stimulus), resulting in a decrease in the magnitude and/or frequency of the conditioned response. Extinction has been applied successfully in the treatment of fear and anxiety disorders; known as exposure therapy, it involves graded exposure to the feared object, situation, or memory in the absence of any aversive event. Attempts to develop an exposure therapy protocol for addicts involving exposure to drug-paired cues without subsequent drug intake have a similar rationale, but thus far have had limited success (Conklin and Tiffany, 2002).

We believe that a better understanding of the behavioral, psychological, and neurobiological mechanisms of extinction will improve the effectiveness of extinction-like

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protocols in the clinic. There already have been great strides in this regard: research on extinction in animal models has revealed major mechanisms, and insights into the role of glutamate—the major excitatory neurotransmitter in the mammalian brain—have led to the development of pharmacotherapeutics to enhance the efficacy of exposure therapy in clinical populations. In this review, we describe what has been learned about the role of glutamate in the extinction of conditioned fear, conditioned drug craving, and conditioned withdrawal, and discuss how those findings have been applied in clinical research. We begin with essential background information on animal models for the study of extinction, terminology and basic behavioral features of extinction, and the neural circuitry of extinction. We then turn to the literature on glutamate actions in extinction at its three major receptor subtypes: *N*-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and metabotropic glutamate receptors (mGluRs). Finally, we consider how these findings have been applied clinically and how they might continue to inform clinical research and practice in the future.

EXTINCTION: FUNDAMENTAL CONCEPTS

Pavlovian conditioning is a form of associative learning in which a conditioned stimulus that predicts the occurrence of an unconditioned stimulus comes to elicit a conditioned response. For example, Pavlov (1927) observed that dogs presented with the sound of a metronome (conditioned stimulus) followed by delivery of food (meat powder; unconditioned stimulus) came to exhibit salivation (conditioned response) to the sound of the metronome alone. Since then, innumerable types of conditioned responses, in species ranging from invertebrates to humans, have been observed. These include both conditioned autonomic responses such as salivation and more complex responses, such as fear evoked by cues associated with trauma in PTSD and drug craving in the presence of drug-related cues in addicts (Heather *et al*, 1991; Rothbaum and Davis, 2003).

Pavlov (1927) observed that conditioned salivation decreased when dogs were exposed repeatedly to the metronome without being given the meat powder. Known as extinction, this decrease in the magnitude and/or frequency of a conditioned response occurs with repeated or prolonged exposure to the conditioned stimulus in the absence of the unconditioned stimulus. All types of conditioned responses are subject to extinction; in the case of emotional conditioned responses such as fear or drug craving, extinction can be conceptualized as reducing the strength of the conditioned response and thereby re-establishing some control.

Modern extinction research makes extensive use of animal models and has uncovered a great deal about the behavioral characteristics, psychological mechanisms, and neurobiology of extinction. A major theme running through the extinction literature is that although extinction is procedurally simple, it is mechanistically complex. For example, among the putative psychological mechanisms underlying extinction are attentional modulation, habituation-like processes, contextual conditioning, modulation of the strength of associations between the conditioned stimulus and the conditioned response, and changes in the activation threshold of the unconditioned stimulus representation (for a review, see Delamater, 2004). Extinction also likely involves an error correction process in which a discrepancy between the actual and predicted unconditioned stimulus results in a proportional decrease in the strength of the association between the conditioned stimulus and the unconditioned stimulus (Rescorla and Wagner, 1972; Wagner and Rescorla, 1972). The error correction view has been particularly well-studied and leads to strong predictions about the conditions under which extinction occurs; for example, it correctly predicts that extinction will not occur when a conditioned stimulus is nonreinforced in compound with a conditioned inhibitor (defined as a cue that has been trained separately to predict the omission of the unconditioned stimulus), because the discrepancy between the actual unconditioned stimulus and the predicted unconditioned stimulus is zero (Rescorla, 2003; Soltysik *et al*, 1983). The error correction view also is supported by neurobiological evidence, including findings that dopamine signaling originating in the midbrain (Schultz and Dickinson, 2000) and activity of the inferior olive-climbing fiber system in the cerebellum (Robleto *et al*, 2004) corresponds to an error signal very much like that envisioned by error correction-based mathematical models of Pavlovian conditioning, such as the Rescorla-Wagner model (1972).

Extinction in Animal Models

Both Pavlovian conditioned responses and instrumental responses (defined as behaviors maintained by a response-contingent outcome, such as delivery of food) are subject to extinction. In general, extinction of one or the other type of response is studied using a specialized animal model, although some models include elements of both. In this review, we are interested primarily in the extinction of Pavlovian conditioned responses as observed in animal models appropriate for the study of conditioned fear, drug seeking, and withdrawal. This focus has implications in terms of the types of cues and responses involved in the studies we will describe. With regard to cues, we define Pavlovian conditioned stimuli as elements of a contingency in which conditioned stimulus presentation predicts unconditioned stimulus delivery, independent of any behavior on the part of the subject. We are not concerned with other, similar types of cues that operate through different mechanisms; these include discriminative stimuli and occasion setters, which are cues that signify that a contingency between other events (a response and an

outcome, or a conditioned stimulus and an unconditioned stimulus) is in effect. With regard to the response, we are interested in Pavlovian conditioned responses to Pavlovian conditioned stimuli, as we have defined them. We will not consider extinction of other kinds of responses—most notably instrumental responses—even if the two types of extinction occur within the same paradigm. An example is extinction of lever pressing for a drug of abuse in the intravenous (IV) drug self-administration paradigm (see below), which is an instrumental response. We will not discuss the mechanisms of this kind of extinction, but we will discuss extinction of conditioned stimulus-induced drug craving (defined operationally as described below) within this paradigm, which is a Pavlovian conditioned response.

Most extinction studies focus on conditioned fear responses, but the literature on extinction of conditioned drug craving and withdrawal is growing (Myers and Carlezon, 2010b). The most commonly used animal models for studying these types of responses are Pavlovian fear conditioning, IV drug self-administration, and place conditioning. In each, there is an initial phase of training (known as acquisition) in which an animal (often a rat or a mouse) learns an association between a cue (conditioned stimulus) and a salient event (unconditioned stimulus). Extinction occurs in a subsequent phase of training in which the animal is exposed to the conditioned stimulus in the absence of the unconditioned stimulus.

In the Pavlovian fear conditioning paradigm, acquisition occurs when an animal is presented with a cue such as a light or tone, followed by an aversive stimulus, such as foot shock. After one or more pairings of these events, the animal exhibits fear in the presence of the cue. In rodents, fear is defined operationally in any of several ways; the most common measures are freezing (cessation of all bodily movements, except those required for respiration) and fear-potentiated startle (an increase in the amplitude of the acoustic startle response when startle is elicited in the presence of a fear-eliciting cue *vs* in its absence). Extinction of conditioned fear occurs when the animal is exposed repeatedly to the conditioned stimulus in the absence of the unconditioned stimulus, and consists of a decrease in the magnitude and/or frequency of the behavioral index of fear.

In the IV drug self-administration paradigm, acquisition occurs over the course of several sessions in which an animal learns to emit an operant response (typically a lever press), which is reinforced by an IV infusion of a drug of abuse. A multimodal stimulus consisting of visual (light) and auditory (tone) components occurs simultaneously with drug infusions and serves as the conditioned stimulus. Cues established in this manner are believed to elicit conditioned drug craving, which is defined operationally as sustainment or reinstatement of drug-seeking behavior (lever pressing) when the cue is presented. Extinction of cue-elicited drug craving occurs over the course of one or more test sessions in which the animal is given access to the lever and the cues are presented periodically but drug delivery is discontinued. Behaviorally, extinction consists of a reduction in cue-elicited drug seeking.

The place conditioning paradigm involves a two- or three-chambered apparatus in which the chambers are distinguished by wall color, floor texture, or both. Typically, the apparatus is configured such that a population of subjects shows no inherent preference for one or the other chamber during a pretraining test in which they are permitted to explore freely. Acquisition occurs when an animal is confined in one of the chambers (which serves as the conditioned stimulus) after an injection of a drug of abuse or a drug that precipitates withdrawal in drug-dependent animals. The drug-paired context thus acquires motivational significance, which is shown in a post-training test in which the animal is once again given the opportunity to explore the apparatus freely. Animals showing conditioned place preference spend more time in the drug-paired chamber than in the alternate chamber, whereas animals showing conditioned place avoidance spend less time in the withdrawal-paired chamber than in the alternate chamber. Extinction of this approach or avoidance response can occur in either of two ways: the animal can be given free access to the place conditioning apparatus in repeated test sessions, or the animal can be confined in the formerly drug- or withdrawal-paired context in the absence of drug administration or precipitated withdrawal (ie, after an injection of saline) and subsequently given free access tests to assess extinction. When extinction has occurred, the animal no longer exhibits a preference for or an aversion to the previously drug- or withdrawal-paired chamber; that is, it spends approximately equal amounts of time in each.

Terminology and Behavioral Features of Extinction

The term 'extinction' can be used to describe both a behavioral training protocol and the outcome of exposure to that protocol. As a way of disambiguating this term, we will refer to the experimental protocol of presenting the conditioned stimulus in the absence of the unconditioned stimulus as extinction training and the observed decrease in the magnitude and/or frequency of the conditioned response as extinction. As there is ample evidence that they are mediated by different mechanisms, a further distinction is made between within-session extinction, defined as extinction occurring during extinction training, and extinction retention, defined as extinction memory assessed at some point after the completion of extinction training (typically at least 24 h). Extinction, like other forms of learning and memory, involves encoding, consolidation, and retrieval/expression phases, which are mediated by different neural mechanisms (Box 1).

A critical insight that has emerged from behavioral studies of extinction is that extinction is not due to forgetting, 'unlearning,' or erasure of the significance of the conditioned stimulus. Pavlovian conditioned responses are long-lasting and resistant to forgetting, such that

Box 1 Extinction-related terminology

Conditioned response. A particular response or internal state elicited by a conditioned stimulus.

Conditioned stimulus. An initially neutral cue that is paired with an unconditioned stimulus and consequently acquires the ability to elicit a conditioned response.

Erasure. A putative extinction mechanism in which memory/synaptic plasticity underlying the conditioned stimulus-unconditioned stimulus association is reversed. Generally considered not to be a viable extinction mechanism because extinguished conditioned responses can reappear under some circumstances after extinction (see relapse effects) indicating that the memory remains at least partially intact. However, recent evidence that fear extinction involves synaptic depotentiation within BLA suggests that erasure may be one of multiple extinction mechanisms.

Extinction. A decline in the magnitude and/or frequency of a conditioned response after exposure to an extinction training protocol.

Extinction retention. Extinction memory assessed at some point after the completion of extinction training (generally at least 24 h).

Extinction training. A behavioral training protocol involving repeated or prolonged exposure to a conditioned stimulus in the absence of the unconditioned stimulus.

Forgetting. Passive loss or degradation of memory for a conditioned stimulus-unconditioned stimulus association. Extinction is distinguishable from forgetting in that extinction requires extinction training to occur, whereas forgetting occurs over time in the absence of further training.

Inhibition. A putative extinction mechanism in which memory for the conditioned stimulus-unconditioned stimulus association remains intact but conditioned response expression is actively inhibited in a context- and time-dependent manner.

Long-term extinction. Extinction memory assessed in an extinction retention test.

Relapse effects. Circumstances under which extinguished conditioned responses reappear. Relapse effects include reinstatement, renewal, and spontaneous recovery.

Reinstatement. Reappearance of an extinguished conditioned response after exposure to the unconditioned stimulus in the absence of the conditioned stimulus.

Renewal. Reappearance of an extinguished conditioned response in an extinction retention test that is conducted in a context different from that of extinction training.

Short-term extinction. A phase of extinction memory assessed during extinction training as within-session extinction.

Spontaneous recovery. Reappearance of an extinguished conditioned response with the passage of time after extinction training.

Unconditioned stimulus. A biologically significant stimulus such as pain due to foot shock, the onset of drug effects, or drug withdrawal, which produces a particular response or internal state. Pairing an unconditioned stimulus with a neutral stimulus (conditioned stimulus) elicits a response or internal state (conditioned response) that is often (but not always) similar to that produced by the unconditioned stimulus.

Within-session extinction. Extinction occurring during extinction training.

without exposure to the conditioned stimulus in the absence of the unconditioned stimulus, the conditioned response does not disappear (Myers and Carlezon, 2010a; Stinus *et al*, 2000; Quirk, 2002). On the other hand, extinction memory is fragile in that extinguished conditioned responses are subject to recovery under several circumstances. For example, exposure to the unconditioned stimulus alone (ie, in the absence of the conditioned stimulus) after the completion of extinction training can be sufficient to restore the conditioned response, a phenomenon known as reinstatement (Rescorla and Heth, 1975). Similarly, exposure to the conditioned stimulus outside the context of extinction training results in a reappearance of the conditioned response, a very robust and reliable effect known as renewal (Bouton and Bolles, 1979; Chaudhri *et al*, 2008). Finally, extinguished conditioned responses re-emerge over time after extinction training, an effect known as spontaneous recovery (Brooks *et al*, 2004; Millin and Riccio, 2002; Pavlov, 1927; Quirk, 2002). Reinstatement, renewal, and spontaneous recovery collectively are known as recovery effects and indicate that extinction does not undo original learning, but is itself a form of new learning in which the conditioned response is suppressed in a context- and time-dependent manner (Bouton, 1993). However, because 'recovery' is a clinical term used to describe the beneficial outcome of treatments for psychiatric disorders, including treatments involving extinction protocols, we will describe reinstatement, renewal, and spontaneous recovery as measures of relapse rather than recovery.

Neural Circuitry of Extinction

Extensive work in the fear conditioning paradigm, primarily, has begun to reveal critical elements of the neural circuitry underlying extinction (Figure 1). A model has emerged in which interactions among three key components—the amygdala, medial prefrontal cortex (mPFC), and hippocampus—mediate extinction learning and memory and its modulation by context (Quirk and Mueller, 2008). A small but growing literature suggests that a similar scenario is likely to be true in addiction as well (Myers and Carlezon, 2010b; Peters *et al*, 2009), but our discussion in this section will draw primarily from the much more extensive fear extinction literature.

The amygdala is a macrostructure that is the cornerstone of the extinction process. In particular, the basolateral complex (BLA; lateral and basolateral nuclei) and the GABAergic intercalated cell masses (ICMs) that gate impulse traffic from BLA to the central nucleus of the amygdala (CeA) are critical. Individual BLA neurons fire selectively to extinguished cues both as extinction training progresses (Herry *et al*, 2008) and after extinction training is complete, in a context-dependent manner (Herry *et al*, 2008; Hobin *et al*, 2003). Pre-extinction training inactivation of the basal nucleus (Herry *et al*, 2008) or post-extinction training lesions of the ICMs (Likhtik *et al*, 2008) impair within-session extinction and extinction retention, respectively (also see Fuchs *et al*, 2002, 2006). Both encoding and consolidation of extinction memory can be modulated by intra-BLA infusions of a wide variety of drugs, including

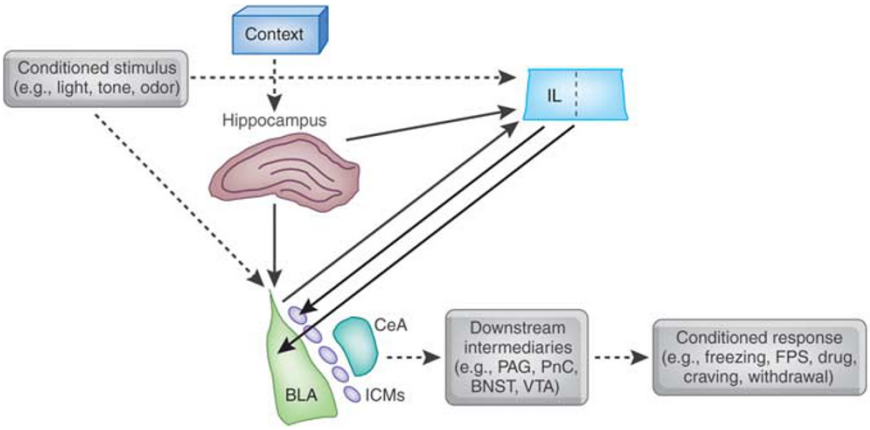

Figure 1. Highly simplified schematic depicting the interactions among the amygdala, infralimbic (IL) region of the medial prefrontal cortex, and hippocampus that are believed to underlie extinction of conditioned fear and, perhaps, extinction of conditioned drug craving and withdrawal as well. The basolateral complex of the amygdala (BLA) is a site of essential plasticity underlying fear memories. BLA receives sensory information about discrete conditioned stimuli, such as lights, tones, and odors, as well as (through the hippocampus) contextual or spatial cues. After acquisition, BLA triggers conditioned fear responses through its projections to the central nucleus of the amygdala (CeA), which in turn innervates hypothalamic and brainstem targets (such as the periaqueductal gray (PAG) and nucleus reticularis pontis caudalis (PnC)) to elicit behavioral indices of fear, including freezing and fear-potentiated startle (FPS). In extinction, the omission of the unconditioned stimulus is detected through a mechanism that is not well understood. CS-related information is relayed to both BLA and IL, and NMDA receptor-dependent synaptic plasticity occurs at both sites. After extinction training is complete, IL contributes to the suppression of fear conditioned responses by inhibiting amygdalar throughput, likely by activating GABAergic interneurons within BLA, GABAergic intercalated cell masses (ICMs) lying between BLA and CeA, or both. A similar scenario may be true for extinction of conditioned drug craving and withdrawal. Drug-related conditioned responses presumably are triggered through different neural intermediaries (such as the ventral tegmental (VTA) or bed nucleus of the stria terminalis (BNST)) than is conditioned fear, but the same basic BLA–mPFC circuitry may be shared, as suggested by findings that NMDA receptor-mediated synaptic plasticity within BLA and mPFC contribute to extinction of cue-induced drug-seeking behavior.

neurotransmitter receptor agonists and antagonists (Akirav, 2007; Berlau and McGaugh, 2006; Botreau *et al*, 2006; Falls *et al*, 1992; Feltenstein and See, 2007; Harris and Westbrook, 1998; Hikind and Maroun, 2008; Kim *et al*, 2007b; Laurent *et al*, 2008; Laurent and Westbrook, 2008; Ledgerwood *et al*, 2003; Lee and Kim, 1998; Lee *et al*, 2006; Lin *et al*, 2003b; Mao *et al*, 2006, 2008; Paolone *et al*, 2009; Roche *et al*, 2007; Schroeder and Packard, 2003, 2004; Sotres-Bayon *et al*, 2007, 2009; Yang *et al*, 2006; Walker *et al*, 2002), as well as modulators of downstream second messengers, transcription, and translation (Lin *et al*, 2003a, 2003b; Lu *et al*, 2001). Extinction alters the phosphorylation state of second messengers and gene expression patterns within BLA (Cannich *et al*, 2004; Chhatwal *et al*, 2005, 2006; Heldt and Ressler, 2007; Herry and Mons, 2004; Lin *et al*, 2003a, 2003b), and manipulation of gene expression within BLA before extinction training modulates extinction memory consolidation (Chhatwal *et al*, 2006). Hence, the amygdala is a central locus underlying the encoding, consolidation, and expression of extinction memory.

The mPFC sends dense projections to the amygdala that terminate, in part, on GABAergic interneurons in BLA and on the ICMs (Berretta *et al*, 2005; Quirk *et al*, 2003; Rosenkranz and Grace, 2001, 2002; Rosenkranz *et al*, 2003). Hence, mPFC is in a position to exert inhibitory control over amygdalar throughput, a possible extinction mechanism (Quirk and Mueller, 2008), at least under some circumstances (cf. Garcia *et al*, 2006; Gewirtz *et al*, 1997). Electrolytic lesions (Quirk *et al*, 2000) or localized inactivation (Sierra-Mercado *et al*, 2006) of the infralimbic (IL) region of mPFC impair extinction retention while having little to no effect on acquisition or within-session extinction, suggesting a role for this region specifically in consolidation and/or expression of extinction memory (also see Hsu and Packard, 2008). Single units within IL fire selectively to presentations of a previously fear conditioned cue during an extinction retention test 24 h after extinction training but not during the extinction training session itself (Milad and Quirk, 2002). Pre-extinction training, intra-mPFC or intra-IL infusions of neurotransmitter receptor agonists or antagonists (Burgos-Robles *et al*, 2007; Hikind and Maroun, 2008; Laurent and Westbrook, 2008; Mueller *et al*, 2008; Pfeiffer and Fendt, 2006; Sotres-Bayon *et al*, 2009; Zushida *et al*, 2007), as well as modulators of downstream second messengers, transcription, and translation (Hugues *et al*, 2004, 2006; Mueller *et al*, 2008; Santini *et al*, 2004), modulate extinction retention without affecting within-session extinction. Immediate post-extinction training administration of many of these agents has a similar effect. When IL microstimulation is paired with presentations of a previously fear conditioned cue in nonextinguished animals, freezing to those cues is attenuated (Milad and Quirk, 2002; Milad *et al*, 2004). Collectively, these findings indicate that mPFC has a significant role in many cases in extinction memory consolidation and expression, likely by its interactions with the amygdala.

The hippocampus also sends dense projections to the amygdala (Pitkanen *et al*, 2000) and substantially innervates mPFC as well (Jay and Witter, 1991). The hippocampus has long been known to mediate spatial and contextual memory (Kim and Fanselow, 1992; Morris *et al*, 1982), and consistent with this, a role for it in the context dependence of extinction has emerged. When hippocampal function is intact throughout acquisition and extinction training, lesions or temporary inactivation of the hippocampus before an extinction retention test block renewal of extinguished freezing when that test occurs outside of the extinction training context (Corcoran *et al*, 2005; Corcoran and Maren, 2001, 2004; Hobin *et al*, 2006; Ji and Maren, 2008; Maren and Hobin, 2007). In other words, contextual modulation of extinction memory expression is diminished in the absence of hippocampal input. This effect is not restricted to behavioral indices of conditioned fear, but is seen with conditioned stimulus-evoked single-unit responses in BLA as well, such that hippocampal inactivation before an extinction retention test blocks the contextual renewal of conditioned stimulus-related single-unit firing (Maren and Hobin, 2007). On the other hand, temporary inactivation of the hippocampus before extinction training enhances the contextual sensitivity of extinction memory, such that renewal is observed in a subsequent extinction retention test even when that test is conducted in the same context as extinction training (Corcoran *et al*, 2005). One possible interpretation of this finding is that prevention of contextual encoding by the hippocampus during extinction training causes the extinction context not to be recognized as such when hippocampal functionality is restored, leading to renewal. Taken together, these findings indicate that the hippocampus is responsible for encoding contextual information during extinction training and subsequently using that information to promote or impede expression of extinction memory, as appropriate, perhaps by its interactions with the amygdala and mPFC.

NMDA RECEPTORS

The NMDA receptor is an ionotropic receptor that has the unique feature of being doubly gated, requiring both membrane depolarization and ligand binding for activation (Seeburg *et al*, 1995). NMDA receptors are located throughout the brain and are heterotetramers comprising two obligatory NR1 subunits and two subunits from the NR2 family (denoted NR2A–D) or the more recently discovered NR3 family. They are implicated heavily in learning, memory, and experience-dependent forms of synaptic plasticity, such as long-term potentiation (LTP) (Nicoll and Malenka, 1999), with NR2A- and NR2B-containing NMDA receptors being particularly important in this regard. Subunit composition greatly influences receptor properties; for example, NR2A-containing receptors have lower glutamate affinity, faster kinetics, and greater channel open probability than do NR2B-containing receptors (Cull-Candy and Leszkiewicz, 2004). Functional differences between NR2A- and NR2B-containing receptors have been noted as well (Walker and Davis, 2008), although the nature of these differences is highly dependent on the brain region and developmental stage in question.

The NMDA receptor was the first of the glutamate receptors to be implicated in extinction and continues to be the most thoroughly studied. Owing to the size of the literature, we will consider studies involving NMDA receptor antagonism, positive modulation of NMDA receptor function, and modulation of NMDA subunit expression in separate subsections.

NMDA Receptor Antagonism

Studies involving systemic administration of NMDA receptor antagonists before fear extinction training report dose-dependent impairments of both within-session extinction and extinction retention (Baker and Azorlosa, 1996; Chan and McNally, 2009; Cox and Westbrook, 1994; Dalton *et al*, 2008; Kelamangalath *et al*, 2007; Lee *et al*, 2006; Liu *et al*, 2009; Santini *et al*, 2001; Sotres-Bayon *et al*, 2007, 2009; Storsve *et al*, 2010; Walker *et al*, 2002) (Table 1). Systemic NMDA receptor antagonists also impair extinction retention or reinstatement when administered immediately after extinction training (Burgos-Robles *et al*, 2007; Laurent *et al*, 2008; Johnson *et al*, 2000; Laurent and Westbrook, 2008; Liu *et al*, 2009; Santini *et al*, 2004; Sotres-Bayon *et al*, 2009) (Table 1), indicating that NMDA receptors are involved in consolidation as well as encoding of extinction memory.

NMDA receptors within BLA and IL contribute to different aspects or phases of fear extinction. Microinfusions of NMDA receptor antagonists into BLA before fear extinction training impair both within-session extinction and extinction retention (Falls *et al*, 1992; Feltenstein and See, 2007; Laurent *et al*, 2008; Laurent and Westbrook, 2008; Lee and Kim, 1998; Lin *et al*, 2003b; Sotres-Bayon *et al*, 2007). However, local infusions of NMDA 2A and 2B antagonists into BLA block the expression of several fear-related conditioned responses, including freezing, suggesting that these drugs could artifactually block extinction retention by interfering with synaptic transmission. Arguing against this possibility is the observation that infusions of ifenprodil, an NMDA 2B-preferring antagonist that does not block expression of fear conditioned responses, also blocks extinction retention (Laurent *et al*, 2008; Laurent and Westbrook, 2008; Sotres-Bayon *et al*, 2007). Immediate post-extinction training intra-BLA infusions of ifenprodil have no effect on subsequent extinction retention when extinction of fear is measured (Laurent and Westbrook, 2008; Sotres-Bayon *et al*, 2009), but similar intra-BLA infusions of AP5 do impair extinction retention when cocaine conditioned place preference is measured (Feltenstein and See, 2007). This suggests that NMDA receptor-dependent synaptic plasticity within BLA is

TABLE 1 Studies Employing NMDA Receptor Antagonists

Species	Test	Drug type	Drug, dose	Locus	Time of admin.	Effect	Reference
Rat	FC-cue-FPS	NR2A, 2B com.	AP5, 1.25-10 μg/side	BLA	Pre-ext	Impaired ext ret.; NE on CR expression	Falls et al. (1992)
Rat	FC-ctx-analgesia	Noncom.	MK-801, 0.025-0.1mg/kg	Sys.	Pre-ext	Impaired ext ret.; NE on CR expression; not state-dep.	Cox and Westbrook (1994)
Rat	FC-cue-lick suppr.	Noncom.	MK-801, 0.025-0.1 mg/kg	Sys.	Pre-ext	Impaired ext ret.; not state-dep.	Baker and Azorlosa (1996)
Rabbit	Eyeblink	Noncom.	MK-801, 0.05.-0.1 mg/kg	Sys.	Pre-ext	Impaired ext; impaired CR expression	Kehoe et al. (1996)
Rat	FC-cue/ctx-freezing	NR2A, 2B com.	AP5, 2.5 μg	BLA	Pre-ext	Impaired ext ret.; impaired CR expression	Lee and Kim (1998)
Rat	FC-ctx-freezing	Noncom.	MK-801, 0.05-0.1 mg/kg	Sys.	Post-ext; prior to unsignaled US	Blocked reinst., prob. due to block of ctx conditioning needed for reinst.	Johnson et al. (2000)
Rat	FC-cue-freezing, CER	NR2A, 2B com.	CPP, 10mg/kg	Sys.	Pre and 24 hrs post-ext	Impaired ext ret. in test 24 hrs after ext. NE on ext ret. in test 48 hrs after ext unless CPP given again 24 hrs post-ext	Santini et al. (2001)
Rat	FC-cue-FPS	Noncom.(partial)	(±)HA-966, 6 mg/kg	Sys.	Pre-ext	Impaired ext ret.	Walker et al. (2002)
Rat	Inhib. avoidance	Noncom.	AP5, 25 nmoles	CA1	Pre-ext	Impaired ext ret.	Szapiro et al. (2003)
Rat	FC-cue-FPS	NR2A, 2B com.	AP5, 5 μg/side	BLA	Pre-ext	Impaired ext ret.; NE on CR expression	Lin et al. (2003b)
Rat	Inhib. avoidance	NR2A, 2B com.	AP5, 5 μg/side	Hipp.	Pre-ext	Blocked ext ret. if given prior to 1st but not 6th ext training trial	Cammarota et al. (2005)
Rat	FC-cue-freezing	Noncom.	MK-801, 0.1 mg/kg	Sys.	Pre-ext	Impaired ext ret.; impaired CR expression	Lee et al. (2006)
Rat	Inhib. avoidance	NR2A, 2B com.	AP5, 5 μg/side	Entorhinal cortex	Immed. post-ext or 24 hrs post-ext	Drug admin. immed. but not 24 hrs post-ext impaired ext ret.	Bevilaqua et al. (2006)
Rat	FC-cue-freezing	NR2B noncom.	Ifenprodil, 5 mg/kg	Sys.	Pre-ext	Impaired within-sess ext and ext ret.; NE on CR expression	Sotres-Bayon et al. (2007)
			Ifenprodil, 1-5 μg	BLA	Pre-ext	Same as systemic	
		NR2A, 2B com.	CPP, 10mg/kg	Sys.	Pre-ext	NE on within-sess ext; impaired ext ret.	
Rat	FC-cue-freezing	NR2A, 2B com.	CPP, 0.06 mg	vmPFC	Pre-ext	NE on within-sess ext; impaired ext ret. and post-ext burst firing, magnitude of which correlated with ext	Burgos-Robles et al. (2007)
					Immed. post-ext	Impaired ext ret.	
Rat	FC-cue-freezing	Noncom.	MK-801, 0.05-0.2 mg/kg	Sys.	Pre-ext	Impaired ext ret. in 23- but not 16-d old pups; impaired fear acq at both ages	Langton et al. (2007)
Rat	FC-ctx-freezing	NR2A, 2B com.	AP5, 2.5 μg/side	BLA	Pre-ext or pre-re-ext	Impaired ext ret. for 1st but not 2nd ext, unless 1st ext also blocked by AP5; impaired CR expression	Laurent and Westbrook (2008a)
		NR2B noncom.	Ifenprodil, 1 μg/side	BLA	Pre-ext	Impaired within-sess ext and ext ret. for 1st and 2nd ext; NE on CR expression	
Rat	FC-ctx-freezing	NR2B noncom.	Ifenprodil, 1 μg/side	BLA	Pre-ext	Impaired within-sess ext and ext ret., 1st and 2nd ext	Laurent and Westbrook (2008b)
				BLA	Immed. post-ext	NE	
			Ifenprodil, 2 μg/side	vmPFC	Pre-ext	Impaired ext ret. for 1st and 2nd ext; NE on within-sess ext	
				vmPFC	Post-ext	Impaired ext ret. for 1st and 2nd ext	
Rat	FC-cue-freezing	NR2B noncom.	Ro 25-6981, 6 mg/kg	Sys.	Pre-ext	Impaired within-sess ext but not ext ret.	Dalton et al. (2008)
Rat	FC-cue-freezing	Noncom.	MK-801, 0.1 mg/kg	Sys.	Pre-ext	Impaired ext ret. for 1st but not 2nd ext; blocked CR expression. Impaired 2nd ext if CS made more novel (via fewer ext trials, new ctx). NE on 1st ext if CS made more familiar (via CS or ctx pre-exposure). Conclude that MK-801 impairs ext for relatively novel CSs but not for relatively familiar CSs.	Chan and McNally (2009)
Rat	FC-cue-freezing	Noncom.	MK-801, 0.3 mg/kg	Sys.	Pre or post-ext	Drug admin. pre- or 4 hrs post-ext but not 12 hrs post-ext impaired ext ret. out to 20 d	Liu et al. (2009)
Rat	FC-cue-freezing	NR2B noncom.	Ifenprodil, 5 mg/kg	Sys.	Immed. post-ext	Impaired ext ret.	Sotres-Bayon et al. (2009)
			Ifenprodil, 2 μg	vmPFC	Pre-ext	NE	
				vmPFC	Immed. post-ext	Impaired ext ret.	
			Ifenprodil, 1 μg/side	BLA	Immed. post-ext	NE on ext ret.	
Rat	FC-cue-freezing	Noncom.	MK-801, 0.1 mg/kg	Sys.	Pre- or post-US habituation	Impaired ability of US habituation (an extinction-like procedure) to reduce CR magnitude if drug given pre- but not 4 hrs post-US habituation	Storsve et al. (in press)
Rat	Cocaine IVSA	NR2A, 2B com.	AP5, 3 μg/side	BLA	Immed. post-ext	Impaired ext. ret.	Feltenstein and See (2007)
Rat	Cocaine IVSA	NR2A, 2B com.	CPP, 5 mg/kg	Sys.	Pre-ext	NE on rate of ext; increased susceptibility to cocaine-induced reinst.	Kelamangalath et al. (2007)
Rat	Amphet. cond. PP	NR2A, 2B com.	AP5, 1.25-5 μg/side	mPFC	Pre-ext	Impaired ext retention	Hsu and Packard (2008)

Abbreviations: acq, acquisition; admin, administration; amphet, amphetamine; BLA, basolateral amygdala; com, competitive antagonist; cond, conditioned; CPA, conditioned place aversion; CR, conditioned response; ctx, context; dep, dependent; ext, extinction; FC, fear conditioning; FPS, fear-potentiated startle; hipp, hippocampus; immed, immediate; inhib, inhibitory; IVSA, intravenous self-administration; mPFC, medial prefrontal cortex; NE, no effect; noncom, noncompetitive antagonist; PP, place preference; pos, positive; prob, probably; reinst, reinstatement; ret, retention; sess, session; suppr., suppression; sys, systemic; vmPFC, ventromedial prefrontal cortex.

involved in encoding fear extinction memory, but that NR2B-containing NMDA receptors within BLA are not required for consolidation, at least for conditioned fear. With regard to IL, pre-extinction training infusions of NMDA receptor antagonists into IL but not the neighboring prelimbic cortex have no effect on within-session extinction but generally impair later extinction retention (Burgos-Robles *et al*, 2007; Laurent and Westbrook, 2008, 2009a; but see Sotres-Bayon *et al*, 2009). Immediate post-extinction infusions of NMDA receptor antagonists into IL block extinction retention consistently (Burgos-Robles *et al*, 2007; Laurent and Westbrook, 2008; Sotres-Bayon *et al*, 2009), providing strong evidence that NMDA receptor-dependent synaptic plasticity within IL is primarily involved in the consolidation of extinction memory.

Interestingly, the contribution of NMDA receptors to fear extinction shifts somewhat when a cue is extinguished a second time; that is, when the experimental protocol involves fear acquisition and extinction, followed by reacquisition and re-extinction of the same cue. Systemic administration of the NMDA receptor antagonist MK-801 before re-extinction training does not impair subsequent extinction retention, unless re-extinction and the extinction retention test occur in a context different from that of initial acquisition and initial extinction (Chan and McNally, 2009). This may result from a more general phenomenon, namely that NMDA receptor activation is required when extinction events are relatively novel but not when they are relatively familiar (Chan and McNally, 2009). Thus, systemic administration of MK-801 does block second extinction if the re-extinguished conditioned stimulus or the context of re-extinction training is relatively novel by virtue of fewer extinction trials or a shift in context. Conversely, MK-801 fails to block first extinction if the extinguished conditioned stimulus or the context of extinction training is relatively familiar by virtue of pre-exposure to the conditioned stimulus or context. On the other hand, novelty does not seem to matter for fear conditioning itself because AP5 blocks fear acquisition in both a novel and a familiar context (Lee and Kim, 1998; Laurent and Westbrook, 2009b). Effects with localized infusions of NMDA receptor antagonists before second extinction are complex. Intra-BLA infusions of AP5 before re-extinction training have no effect on subsequent extinction retention; however, infusions of ifenprodil impair both within-session extinction and extinction retention (Laurent *et al*, 2008; Laurent and Westbrook, 2008). Interestingly, intra-BLA infusions of AP5 do block re-extinction if initial extinction was also blocked by intra-BLA AP5 (Laurent *et al*, 2008), as if blockade of the first extinction restored the sensitivity of the second extinction to NMDA receptor blockade. However, this does not seem to hold for localized infusions into mPFC, where either pre-extinction or immediate post-extinction training infusions of ifenprodil block retention of both first and second extinction (Laurent and Westbrook, 2008).

NMDA receptor antagonism impairs extinction not only of fear conditioned responses but also of conditioned drug craving. Intra-mPFC, pre-extinction training infusion of AP5 impairs extinction of amphetamine conditioned place preference (Hsu and Packard, 2008). In the drug IV self-administration paradigm, systemic pre-extinction training administration of the competitive NMDA receptor antagonist CPP is associated with more robust cocaine-induced reinstatement, perhaps indicative of reduced extinction (Kelamangalath *et al*, 2007), and intra-BLA infusions of AP5 immediately after each of several test (ie, cue extinction) sessions leads to more persistent cue-maintained drug-seeking behavior, perhaps because extinction of the response-reinstating or response-maintaining value of the cues is impaired (Feltenstein and See, 2007).

Positive Modulation of NMDA Receptor Function

Whereas antagonism of NMDA receptors impairs extinction, enhancement of NMDA receptor function by the NMDA receptor partial agonist D-cycloserine (DCS) facilitates extinction. DCS acts at the glycine modulatory site on the NR1 NMDA receptor subunit to increase calcium influx without causing damage due to neurotoxicity (Sheinin *et al*, 2001).

In the Pavlovian fear conditioning paradigm, systemic administration of DCS either before (Bouton *et al*, 2008; Weber *et al*, 2007; Hefner *et al*, 2008; Kelley *et al*, 2007; Langton and Richardson, 2008; Ledgerwood *et al*, 2003, 2005; Lee *et al*, 2006; Lin *et al*, 2009a, b; Mao *et al*, 2006, 2008; Myers and Carlezon, 2010a; Tomilenko and Dubrovina, 2007; Walker *et al*, 2002; Weber *et al*, 2007; Woods and Bouton, 2006; Yamada *et al*, 2009; Yang and Lu, 2005) or after (Ledgerwood *et al*, 2003, 2004, 2005; Parnas *et al*, 2005; Weber *et al*, 2007; Werner-Seidler and Richardson, 2007) extinction training facilitates extinction (Table 2). Similarly, mutant mice with a single point mutation in the gene encoding D-amino acid oxidase, a catabolic enzyme of D-serine (an endogenous ligand at the NR1 glycine modulatory site), show increased whole-brain D-serine concentrations and facilitated extinction of freezing to contextual, but not auditory, cues (Labrie *et al*, 2009). Immediate post-extinction injection of spermine, another positive modulator of the NMDA receptor, into the hippocampus facilitates extinction of the inhibitory avoidance response (Gomes *et al*, 2010). To our knowledge, no published studies have examined the effect of DCS infusions directly into IL, but local infusion of DCS into BLA before (Akirav, 2007; Lee *et al*, 2006; Mao *et al*, 2006, 2008; Walker *et al*, 2002) or after (Ledgerwood *et al*, 2003) fear extinction training mimics the effects of systemic administration.

DCS may be more effective under some circumstances than others (Table 3). For example, there is a growing body of evidence to suggest that DCS reverses fear extinction deficits that are observed after stress (Akirav, 2007; Matsumoto *et al*, 2008; Nic Dhonnchadha *et al*, 2010; Yamamoto *et al*, 2008), alcohol withdrawal (Bertotto *et al*, 2006), or REM sleep deprivation (Silvestri and Root, 2008);

TABLE 2 Studies Employing NMDA Receptor Agonists or Other Positive Modulators

Species	Test	Drug type	Drug, dose	Locus	Time of admin.	Effect	Reference
Rat	FC-cue-FPS	Partial ag.	DCS, 3.25 - 30mg/kg	Sys.	Pre-ext	Facilitated ext ret.	Walker et al. (2002)
			DCS, 10 μg/side	BLA	Pre-ext	Same as systemic	
		Antag. + partial ag.	(±)HA-966, 6 mg/kg + DCS, 15 mg/kg	Sys.	Pre-ext	Co-admin of antag. blocked DCS effect	
Rat	FC-cue-freezing	Partial ag.	DCS, 2.5-10 mg/kg	Sys.	Pre-or post-ext up to 2 hrs	Facilitated ext ret.	Ledgerwood et al. (2003)
			DCS, 10 μg/side	BLA	Immed. post-ext	Same as systemic	
Rat	FC-cue-freezing	Partial ag.	DCS, 15 mg/kg	Sys.	Immed. post-ext	Facilitated ext ret.; impaired reinst.	Ledgerwood et al. (2004)
Rat	FC-cue-freezing	Partial ag.	DCS, 15 mg/kg	Sys.	Immed. post-ext	Generalized ext: DCS + ext to Cue 1 facilitated ext ret. to Cue 1 and Cue 2	Ledgerwood et al.(2005)
Rat	FC-cue-freezing	Partial ag.	DCS, 15 mg/kg	Sys.	Immed. post-ext	Facilitated ext; tolerance to DCS after multiple admins; tolrance dissipated over time	Parnas et al. (2005)
Rat	FC-cue-FPS	Partial ag.	DCS, 15 mg/kg	Sys.	Pre-ext	Facilitated ext ret.; effect blocked by MAPK or PI3K antagonist, transciptional inhibitor, or protein synthesis inhibitor	Yang and Lu (2005)
Rat	FC-cue-CER	Partial ag.	DCS, 15 or 30 mg/kg	Sys.	Pre-ext	Facilitated ext; intact renewal	Woods and Bouton (2006)
Rat	FC-cue-freezing	Partial ag.	DCS, 15 mg/kg	Sys.	Pre-ext	Facilitated ext ret.	Lee et al. (2006)
			DCS, 10 μg/side	BLA	Pre-ext	Same as systemic	
Rat	FC-cue-FPS	Partial ag.	DCS, 10 μg/side	BLA	Pre-ext	Facilitated ext ret. and ext-induced increase in BLA cell surface GluR1 expression	Mao et al. (2006)
Mouse	Inhib. avoidance	Partial ag.	DCS 15 mg/kg	Sys. x 15 d	Pre-ext	Faciliated ext. in low or intermed. anxious mice but not in high anxious	Tomilenko et al. (2007)
Rat	FC-cue-freezing	Partial ag.	DCS, 15 mg/kg	Sys.	Immed. post-ext	Facilitated ext. ret.; effect blocked by prior daily x14 d admin of DCS or imipramine	Werner-Seidler and Richardson (2007)
Rat	FC-cue-freezing	Partial ag.	DCS, 15 mg/kg	Sys.	Immed. post-ext	Facilated ext ret. but only in rats showing some within-sess ext	Weber et al. (2007)
Rat	FC-cue-FPS	Partial ag.	DCS, 15 mg/kg	Sys.	Pre-ext	Reversed disruption of ext ret. by glucocorticoid antag.	Yang and Lu (2007)
			DCS, 5 mg/kg	Sys.	Pre-ext	Facilitated ext. ret: synergistic effect with low dose glucocorticoid	
Rat	CTA	Partial ag.	Muscimol, 0.05 μg/side + DCS, 20 μg/side	BLA	Pre-ext	Blocked impairment of ext ret. by muscimol, a GABA(A) receptor agonist	Akirav (2007)
Rat	FC-cue-FPS	Partial ag.	DCS, 10 μg/side	BLA	Pre-ext	Facilitated ext ret. and ext-induced increase in BLA cell surface GluR1 expression; blocked reinst.	Mao et al. (2008)
Rat	FC-cue-freezing, CER	Partial ag.	DCS 15, or 30 mg/kg	Sys.	Pre-ext	Facilitated ext ret. but only in rats showing some within-sess ext; intact renewal	Bouton et al. (2008)
Rat	FC-cue-FPS	Partial ag.	DCS, 15 mg/kg	Sys.	Pre-ext	Facilitated 1st but not 2nd ext unless 2nd ext involved a different cue	Langton and Richardson (2008)
Mouse	FC-cue-freezing	Partial ag.	DCS, 5,15, 30 mg/kg	Sys.	Pre-ext	Facilitated ext retention in C57BL/6J but not 129S1 mice	Hefner et al. (2008)
Rat	FC-cue-FPS	Partial ag.	DCS, 20 mg/kg	Sys.	Pre-ext	Facilitated ext ret. and ext-induced increase in BLA AMPA/NMDA receptor ratio; effects prevented by endocytosis blocker	Lin et al. (2009)
Mouse	FC-cue-freezing	Partial ag.	DCS, 30 mg/kg	Sys.	Pre-ext	Facilitated ext ret.; impaired reinst.; no effect on 2nd ext	Yamada et al. (2009)
Rat	CPA (morphine W/D)	Partial ag.	DCS, 15 mg/kg	Sys.	Pre-ext	Facilitated ext ret.	Myers and Carlezon (2010)
Rat	FC-cue, ctx-freezing	Pos. mod. via ↑ D-serine	Mutation in catabolic enzyme for D-serine	Sys.	Constitutive	NE on FC; facilitated ext of freezing to context but not cue	Labrie et al. (2009)
Rat	Inhib. avoidance	Partial ag.	Spermidine, 2 nmol	Hipp.	Post-ext	Drug admin. immed but not 6 hrs post-ext faciliated ext ret; effect blocked by co-admin of NR2B antag.	Gomes et al. (in press)
Rat	Bar press for food	Partial ag.	DCS, 3 mg/kg	Sys.	Pre-ext	Impaired within-sess ext.; no drug-free post-test; prob. perf. effect	Port and Seybold (1998)
Rat	Cocaine cond. PP	Partial ag.	DCS, 15 mg/kg	Sys. x 9 d	Post-ext	Facilitated ext if given immed. but not 4 hrs post-ext; blocked relapse at 2 wks (longest interval tested)	Botreau et al. (2006)
			DCS, 10 μg/side	BLA x 3 d	Post-ext	Same as systemic	
Mouse	Cocaine cond. PP	Partial ag.	DCS, 15 mg/kg	Sys.	Pre-ext	May have facilitated ext. and blocked spontaneous recovery; NE on cocaine reinst.	Kelley et al. (2007)
Rat	Amphet. PP	Partial ag.	DCS, 10 μg/side	d. hipp.	Pre-ext	Facilitated ext ret. but also facilitated reacq.	Sakurai et al. (2007)
Rat	Run maze for food	Partial ag.	DCS, 15 mg/kg	Sys.	Immed. post-ext	Faciliated ext	Gabriele and Packard (2007)
Rat	Ethanol IVSA	Partial ag.	DCS, 5 mg/kg	Sys. x 12 d	Pre-ext	Facilitated ext retention 1 day after last ext. session drug free	Vengeliene et al. (2008)
Mouse	Bar press for food	Partial ag.	DCS, 15, 30 mg/kg	Sys. X 8 d or 10 d	Immed. post-ext	Faciliated ext.; efficacy of DCS dependent on interval between ext sessions	Shaw et al. (2009)
Rat	Cocaine cond. PP	Partial ag.	DCS, 15 mg/kg	Sys.	Immed. post-ext	Facilitated ext across days; blocked relapse	Paolone et al. (2009)
Rat	Cocaine IVSA	Agonist	D-serine, 100 mg/kg	Sys.	Pre- or post-ext	NE on ext rate; attenuated cocaine- but not sucrose-induced reinst.	Kelamangalath et al. (2009)
Mouse	Ethanol PP	Partial ag.	DCS, 15-60 mg/kg	Sys. x 12 d	Pre-ext	NE on ext rate; impaired reacq	Groblewski et al. (2009)
Mouse	Cocaine cond. PP	Partial ag.	DCS, 15, 30 mg/kg	Sys. x 8 d	Immed. post-ext	Facilitated ext; 30 mg/kg DCS relapse at 2 weeks compared to saline or 15 mg/kg DCS	Thanos et al. (2009)
Rat	Cocaine IVSA	Partial ag.	DCS, 30 mg/kg	Sys.	Pre or post-ext	Facilitated ext when given immed but not 6 hrs post-ext; retarded reacq	Nic Dhonnchadha et al. (2009)
Monkey	Cocaine IVSA	Partial ag.	DCS, 10 mg/kg	Sys.	Pre-ext	NE on ext; retarded reacq.	

Abbreviations: admin, administration; ag, agonist; amphet, amphetamine; antag, antagonist; BLA, basolateral amygdala; cond, conditioned; CPA, conditioned place aversion; CTA, conditioned taste aversion; ctx, context; d, dorsal; dep, dependent; ext, extinction; FC, fear conditioning; FPS, fear-potentiated startle; hipp, hippocampus; immed, immediate; inhib, inhibitory; IVSA, intravenous self-administration; mod, modulation, mPFC, medial prefrontal cortex; NE, no effect; perf, performance; poss, possible; prob, probable; PP, place preference; pos, positive; reacq, reacquisition; reinst, reinstatement; ret, retention; sess, session; sys, systemic; vmPFC, ventromedial prefrontal cortex; W/D, withdrawal.

TABLE 3 Studies Examining DCS Efficacy in Stressed Animals and Human Clinical and Nonclinical Populations

Species	Test or Disorder	Drug type	Drug, dose	Locus	Time of admin.	Effect	Reference
Rat	FC-ctx-freezing	Partial ag.	DCS, 5 mg/kg	Sys.	Post-ext (1-180 min)	DCS facilitated ext ret. in rats withdrawn from ethanol; reduced reinst.	Bertotto et al. (2006)
Rat	FC-ctx-freezing	Partial ag.	DCS, 15 mg/kg	Sys. x 6 d in HC water	Pre-ext	Stress impaired ext and NMDA receptor subunit expression in hippocampus; both normalized by DCS.	Yamamoto et al. (2008)
Rat	FC-ctx-freezing	Partial ag.	DCS, 15 mg/kg	Sys.	Pre-ext	DCS reversed disruption of ext following early life stress	Matsumoto et al. (2008)
Rat	FC-cue-freezing	Partial ag.	DCS, 30 mg/kg	Sys.	Pre-ext	DCS reversed disruption of ext following REM sleep deprivation; impaired subsequent ext if given immed after FC	Silvestri et al. (2008)
Mouse	CTA	Partial ag.	DCS, 15 mg/kg	Sys.	Pre-ext	DCS reversed disruption of ext in BDNFmet mice and restored Fos expression in vmPFC	Yu et al. (2009)
Rat	FC-ctx-freezing; CTA	Partial ag.	DCS, 20 μg/side	BLA	Pre-ext	Reduced stress-induced impairment of ext. of FC but not CTA	Akirav et al. (2009)
Human	Height phobia	Partial ag.	DCS, 50, 500 mg	Sys.	Pre-ext	Facilitated ext ret. out to 3 months (longest interval tested)	Ressler et al. (2004)
Human	Social phobia	Partial ag.	DCS, 50 mg	Sys.	Pre-ext	Facilitated ext ret. out to 1 month (longest interval tested)	Hofman et al. (2006)
Human	FC-cue-GSR	Partial ag.	DCS, 50 or 500 mg	Sys.	Pre-ext	NE on ext or spontaneous recovery	Guastella et al. (2006)
Human	Spider phobia	Partial ag.	DCS, 50 or 500 mg	Sys.	Pre-ext	NE	Guastella et al. (2007)
Human	OCD	Partial ag.	DCS, 125 mg	Sys.	Pre-ext	Facilitated extinction ret.	Kushner et al. (2007)
Human	OCD	Partial ag.	DCS, 250 mg	Sys.	4 hrs pre-ext	NE; drug given too early?	Storch et al. (2007)
Human	Eating disorders	Partial ag.	DCS, 50 mg	Sys.	Pre-ext	NE on eating behavior; poss. floor effect or lower fear of food in DCS group prior to treatment	Steinglass et al. (2007)
Human	Processing of facial expressions	Partial ag.	DCS, 500 mg	Sys.	Pre-habituation	Reduced activation of amyg. to fearful faces; no habituation over trials, prob. due to floor effect	Britton et al. (2007)
Human	Social anxiety disorder	Partial ag.	DCS, 50 mg	Sys.	Pre-ext	Facilitated ext ret. out to 1 month (longest interval tested)	Guastella et al. (2008)
Human	OCD	Partial ag.	DCS, 100 mg	Sys.	Pre-ext	Facilitated ext ret. out to 1 month (longest interval tested)	Wilhelm et al. (2008)
Human	Nicotine addiction	Partial ag.	DCS, 50 mg	Sys.	Pre-ext	Facilitated within-sess ext of GSR and craving; reduced expired CO_2 at 1-wk follow-up	Santa Ana et al. (2009)
Human	Cocaine addiction	Partial ag.	DCS, 50 mg	Sys.	Pre-ext	DCS increased reactivity to cocaine cues; trend towards facilitation of ext ret.	Price et al. (2009)
Human	FC-cue-FPS	Partial ag.	DCS, 50, 250, 500 mg	Sys.	Pre-ext	NE on ext ret.	Grillon (2009)
Human	Highly anxious patients	Partial ag.	DCS, 50 mg	Sys.	Pre-ext	Facilitated reduction in attentional bias toward threat; NE on emotional reactivity	Behar et al. (in press)
Human	Panic disorder	Partial ag.	DCS, 50 mg	Sys.	Pre-ext	Facilitated ext out to 1 month (longest interval tested)	Otto et al. (2010)

Abbreviations: admin, administration; ag, agonist; BLA, basolateral amygdala; CTA, conditioned taste aversion; ctx, context; ext, extinction; FC, fear conditioning; FPS, fear-potentiated startle; HC, home cage; NE, no effect; ret, retention; sess, session; sys, systemic.

in genetically modified mice that have a polymorphism in the BDNF gene (val-met substitution) (Yu *et al*, 2009); and even when muscimol is infused into BLA (Akirav, 2007). Perhaps consistent with these stress-related effects, DCS interacts with stress hormones: DCS blocks the extinction-impairing effect of the corticosteroid synthesis inhibitor metyrapone and enhances the extinction-facilitating effects of the synthetic glucocorticoid dexamethasone (Yang *et al*, 2007). These observations also may be consistent with findings in clinical studies (described below, in the 'Targeting glutamate clinically: clinical use of DCS' section) that DCS facilitates exposure therapy in clinical, but not in subclinical, populations. Finally, DCS facilitates extinction retention only in rats that show some evidence of within-session extinction during extinction training and not in rats that are resistant to extinction (Bouton *et al*, 2008; Hefner *et al*, 2008; Weber *et al*, 2007), and DCS administered before re-extinction training has no effect, similar to the failure of systemic NMDA receptor antagonists to block re-extinction under many circumstances (Langton and Richardson, 2008).

Yang and Lu (2005) examined the molecular mechanisms underlying DCS-induced facilitation of fear extinction. They found that exposure to a suboptimal extinction training protocol modestly increases phospho-MAPK and phospho-Akt (the activated forms of kinases that have important roles in intracellular signaling cascades) in BLA, and that exposure to this same protocol after administration of DCS leads to more robust increases. Consistent with this, intra-BLA infusions of the MAPK inhibitors U0126 or PD98059 or the PI3K inhibitor wortmannin block the behavioral facilitation of extinction by DCS. Intra-BLA infusions of actinomycin D, a transcriptional inhibitor, and anisomycin, a protein synthesis inhibitor, also block DCS-induced facilitation of extinction. In the 'AMPA receptors' section, we describe other findings indicating that DCS modulates the expression and trafficking of AMPA receptor subunits in BLA (Lin *et al*, 2009a, b; Mao *et al*, 2006; Mao *et al*, 2008).

Extinction of conditioned drug craving and withdrawal is sensitive to DCS as well. Systemic administration of DCS before or immediately after repeated place preference tests, or localized infusion of DCS into the BLA immediately after repeated tests, facilitates extinction of cocaine conditioned place preference (Botreau *et al*, 2006; Paolone *et al*, 2009; Thanos *et al*, 2009). Pre-extinction training systemic administration of DCS also facilitates extinction of naloxone-induced conditioned place aversion in morphine-dependent rats (Myers and Carlezon, 2010a). DCS does not enhance the rate of extinction of ethanol conditioned place preference but retards subsequent reconditioning, suggesting a facilitation of extinction that may have been obscured by floor or performance effects (Groblewski *et al*, 2009); similarly, pre-extinction training DCS dose dependently retards subsequent reacquisition of cocaine seeking in both rats and squirrel monkeys (Nic Dhonnchadha *et al*, 2010; but see Sakurai *et al*, 2007). Finally, in cocaine (Nic Dhonnchadha *et al*, 2010) and ethanol (Vengeliene *et al*, 2008) self-administration paradigms, rats receiving DCS before sessions in which drug delivery was discontinued but response-contingent cues continued to occur stopped responding more rapidly than did rats receiving vehicle, presumably because DCS facilitated extinction of the secondary reinforcing value of the cues. DCS also facilitates extinction of maze running or bar pressing for food (Gabriele and Packard, 2007; Shaw *et al*, 2009). In some of these studies, DCS-facilitated extinction is especially enduring: DCS reduced cocaine-induced reinstatement (Kelamangalath *et al*, 2009; Paolone *et al*, 2009; but see Kelley *et al*, 2007) and retarded spontaneous recovery (Botreau *et al*, 2006; Kelley *et al*, 2007).

Modulation of NMDA Receptor Subunit Expression

Some investigators have noted extinction-related changes in NMDA receptor subunit expression in brain areas including mPFC and hippocampus. In a study examining the effect of previous corticosterone (cort) exposure on subsequent fear learning, cort-exposed rats showed impaired extinction and reduced NR2B expression within vmPFC (Gourley *et al*, 2009). Rats exhibiting the poorest extinction showed the least NR2B expression, suggesting that the extinction deficit could be a product of changes in vmPFC NMDA receptor expression induced by previous cort exposure. Similarly, rats that had undergone maternal separation as pups showed impaired fear extinction and reduced NR1 expression in IL (Wilber *et al*, 2009). In a study involving drug-paired cues, rats that received noncontingent (yoked) administrations of cocaine in an operant chamber and which subsequently were exposed to that chamber in the absence of cocaine showed increased expression of the NR1 subunit in mPFC (Crespo *et al*, 2002). In the hippocampus, contextual fear extinction was found to be associated with decreased expression of NR1, NR2A, and NR2C, and increased expression of NR2B (Yamamoto *et al*, 2008). Finally, transgenic mice with elevated forebrain NR2B expression show facilitated fear extinction (Tang *et al*, 1999), suggesting that genetic manipulations that increase NMDA receptor expression can positively impact extinction.

AMPA RECEPTORS

The AMPA receptor is found throughout the brain and is an ionotropic receptor mediating fast synaptic transmission. AMPA receptors are tetramers composed of subunits designated GluR1-4, which assemble as a 'dimer of dimers.' In addition to its role as a mediator of basal synaptic transmission, the AMPA receptor also is involved in experience-dependent forms of synaptic plasticity (eg, see Carlezon and Nestler, 2002; Malinow and Malenka, 2002).

The literature on the involvement of AMPA receptors in extinction comes almost entirely from studies of fear extinction (Table 4). An early finding was that infusion of the AMPA receptor antagonist CNQX into BLA before

TABLE 4 Studies Examining the Role of AMPA Receptors and Metabotropic Glutamate Receptors

Species	Test	Drug type	Drug, dose	Locus	Time of admin.	Effect	Reference
Rat	FC-cue-FPS	AMPAR antag.	CNQX, 2.5 μg/side	BLA	Pre-ext	NE	Falls et al. (1992)
Rat	FC-cue-FPS	AMPAR antag.	CNQX, 5 μg/side	BLA	Pre-ext	NE	Lin et al. (2003)
Rat	FC-cue-freezing	Interferes with AMPAR endocytosis	Tat-GluR23Y, 15 pmol/side	BLA	Pre-ext	Impaired within-sess ext and subsequent ext ret.	Kim et al. (2007b)
Rat	FC-cue-freezing	Interferes with AMPAR endocytosis	Tat-GluR23Y, 1.5 μg/side	Sys.	Pre-ext	Impaired within-sess ext and subsequent ext ret.	Dalton et al. (2008)
					Pre-ext ret. test	NE	
Mouse	FC-ctx-freezing	AMPAR potentiator	PEPA, 3, 10, or 30 mg/kg	Sys.	Pre-ext	Facilitated wihtin-sess ext and ext ret.	Zushida et al. (2009)
			PEPA, 0.02 μg/side	amyg	Pre-ext	Same as systemic	
			PEPA, 0.02 μl	mPFC	Pre-ext	Nonsig. Trend towards facilitation of within-sess ext and ext ret.	
Mouse	FC-ctx-freezing	AMPAR potentiator	PEPA, 30 mg/kg	Sys.	Pre-ext	Facilitated ext ret.; blocked reinst.; NE on 2nd ext	Yamada et al. (2009)
Mouse	FC-cue-CER	mGluR7 KO	N/A	Sys.	Constitutive	Impaired ext	Callaerts-Vegh et al. (2006)
Rat	FC	mGluR1 antag.	CPCCOEt, 0.3 or 3 μg/side	BLA	Pre-ext	Impaired within-sess ext occurring 48 hrs but not 2 hrs after acq; impaired ext ret. after 48 hr ext	Kim et al. (2007a)
Rat	FC-cue-FPS	mGluR7ag.	AMN082, 3, 10, or 20 mg/kg	Sys.	Pre-ext	Facilitated ext ret.	Fendt et al. (2008)
Mouse	FC-cue-CER	mGluR7 KO	N/A	Sys.	Constitutive	Impaired ext	Goddyn et al. (2008)
Mouse	FC-cue/ctx-freezing	mGluR5 KO	N/A	Sys.	Constitutive	Impaired ext	Xu et al. (2009)
Rat	Cocaine cond. PP	mGluR5 pos. allosteric modulator	CDPPB, 0.3, 3, or 30 mg/kg	Sys.	Pre-ext	Faciliated ext	Gass and Olive (2009)

Abbreviations: BLA, basolateral amygdala; ctx, context; ext, extinction; FC, fear conditioning; FPS, fear-potentiated startle; mPFC, medial prefrontal cortex; N/A, not applicable; NE, no effect; noncom, noncompetitive antagonist; reinst, reinstatement; ret, retention; sess, session; sys, systemic.

extinction training had no effect on subsequent extinction retention (Falls *et al*, 1992). The possibility that the small amount of fear seen in the extinction retention test was due to amygdalar neurotoxicity as opposed to intact extinction was ruled out in a separate experiment, in which rats infused with CNQX without undergoing extinction training showed robust fear in a test conducted at the same post-infusion interval. These findings, which have since been replicated by a different group (Lin *et al*, 2003b), were unexpected and have been somewhat of an enigma in the field, as it is not immediately obvious why blocking the action of glutamate at AMPA receptors in BLA should have no effect, given that BLA activation is considered by most to be critical for fear extinction. However, they do show that extinction can still occur when expression of the conditioned response is blocked, as often occurs with local infusion of AMPA receptor antagonists into BLA (Kim *et al*, 1993).

A recent finding indicates that the AMPA receptor agonist PEPA dose-dependently facilitates contextual fear extinction when administered systemically to mice before extinction training (Yamada *et al*, 2009; Zushida *et al*, 2007). PEPA had a similar facilitatory effect when infused directly into the anterior cingulate/prelimbic region of mPFC and (in a separate experiment) into the basolateral/central amygdala, although the effect size was larger with mPFC infusions (Zushida *et al*, 2007). Consistent with these behavioral findings, electrophysiological and gene expression (qPCR) analyses indicated that GluR3 and GluR4 subunits and flop AMPA receptor splice variants—which are preferred by PEPA—are enriched in mPFC (Zushida *et al*, 2007).

A potential mechanism whereby PEPA might exert its behavioral effect is by promotion of AMPA receptor internalization. Conditioned fear acquisition is associated with increased cell-surface expression of GluR1 and GluR2 subunits in BLA (Rumpel *et al*, 2005); recent reports indicate that fear extinction, under some circumstances, reverses this increase. Kim *et al* (2007a) found decreased cell-surface expression of GluR1 and GluR2 subunits in BLA in extinguished animals relative to that seen in fear-conditioned controls that did not undergo extinction. Similarly, Mao *et al* (2006, 2008) reported decreased cell-surface and increased cytoplasmic GluR1 and GluR2 subunit expression in BLA after extinction, when extinction training occurred soon (1 h) after fear acquisition but not at longer intervals (24–48 h), unless extinction training 24–48 h after acquisition occurred under the influence of DCS. Consistent with these biochemical findings, Lin *et al* (2009a, b) performed whole-cell patch-clamp recordings of BLA neurons in slices obtained from rats that had been fear conditioned and extinguished, and found that increased AMPA/NMDA ratios seen after fear acquisition were reversed after extinction coupled with DCS. Molecular mechanisms of AMPA receptor internalization in extinction include unbinding of GluR subunits from scaffold proteins, including PSD-95 and SAP97 (Mao *et al*, 2008), activation of

the phosphatase calcineurin (Havekes *et al*, 2008; Lin *et al*, 2003a), decoupling of protein kinase A from its anchoring protein AKAP (Isiegas *et al*, 2006; Nijholt *et al*, 2008), and proteolysis (Mao *et al*, 2008).

Recently, a novel tool has become available that can be used to manipulate AMPA receptor internalization directly. Known as $GluR2_{3Y}$, it is a synthetic peptide containing a sequence of amino acids found in the carboxy terminus of the GluR2 subunit that is critical to activity-induced AMPA receptor internalization. By competing with endogenous GluR2 subunits, $GluR2_{3Y}$ largely blocks AMPA receptor internalization and associated forms of synaptic plasticity, including long-term depression and depotentiation (Brebner *et al*, 2005). $GluR2_{3Y}$ can be dialyzed directly into neurons during whole-cell patch-clamp recordings or conjugated to the HIV Tat protein, which allows it to cross cell membranes, permitting intracerebral or even systemic administration. In amygdala slices, $GluR2_{3Y}$ (but not $GluR2_{3A}$, a control construct) blocks the induction of GluR2 internalization (Lin *et al*, 2009a, b) and synaptic depotentiation in slices obtained from fear-conditioned animals (Kim *et al*, 2007a). Behaviorally, systemic administration (Dalton *et al*, 2008) or intra-BLA infusion (Kim *et al*, 2007a) of Tat-$GluR2_{3Y}$ (but not $GluR2_{3A}$) before extinction training impairs within-session extinction and subsequent extinction retention. $GluR2_{3Y}$ had no effect when administered in the absence of extinction training (Kim *et al*, 2007a) or before a test of extinction retention in animals extinguished previously (Dalton *et al*, 2008). Finally, Lin *et al* (2009a, b) found that Tat-$GluR2_{3Y}$ infused into BLA before extinction training blocks DCS-induced facilitation of extinction and the accompanying decrease in AMPA/NMDA ratios.

AMPA receptor binding is sufficient but not necessary for AMPA receptor internalization. There is evidence for NMDA receptor-dependent AMPA receptor endocytosis in cultured hippocampal (Beattie *et al*, 2000) and nucleus accumbens neurons (Mangiavacchi and Wolf, 2004) and in the lateral amygdala *in vitro* (Mao *et al*, 2008; Yu *et al*, 2008). In this light, it may be understandable why pre-extinction training intra-BLA infusions of AMPA receptor antagonists have no apparent effect on extinction: if extinction-related AMPA receptor internalization in BLA *in vivo* were mediated primarily by glutamate binding to NMDA receptors, then AMPA receptor antagonists would not be expected to have an effect. This might provide a mechanism for DCS-induced facilitation of fear extinction: rather than (or in addition to) facilitating extinction-related LTP in BLA, DCS might enhance NMDA receptor-dependent AMPA receptor internalization. Consistent with this, Mao *et al* (2008) found that DCS facilitated NMDA-induced GluR1 and GluR2 internalization in BLA *in vitro*.

AMPA receptor internalization is a mechanism of synaptic depotentiation, a form of synaptic plasticity amounting to a reversal of LTP (Huang and Hsu, 2001). Other evidence for a role of BLA depotentiation in extinction includes the finding that application of depotentiation-inducing stimulation to BLA *in vivo* in previously fear-conditioned animals leads to attenuation of fear memory expression (Lin *et al*, 2003) and that the induction of BLA depotentiation *in vitro* is occluded in slices obtained from extinguished animals (Kim *et al*, 2007a). A puzzle still to be solved in the extinction field is how reversal of BLA LTP—which is believed to underlie fear memory storage (Sigurdsson *et al*, 2007)—can be reconciled with relapse phenomena indicating that extinction is not 'unlearning.' The most likely scenario is that depotentiation is but one of multiple extinction mechanisms. For example, some conditioned stimulus-related single-unit responses in BLA diminish over the course of extinction training, potentially through a depotentiation mechanism, but some persist (Herry *et al*, 2008; Quirk *et al*, 1997; Repa *et al*, 2001) and others develop as extinction training progresses (Herry *et al*, 2008), suggesting that other forms of synaptic plasticity are involved. In addition, modulation of GABAergic (and not just glutamatergic) neurotransmission has a significant role in extinction in that extinction is impaired by administration of a $GABA_A$ receptor inverse agonist (Harris and Westbrook, 1998) or targeted lesions of the ICMs (Likhtik *et al*, 2008) and is associated with increased frequency and amplitude of IPSCs (Lin *et al*, 2009a, b), GABA-related gene expression (Chhatwal *et al*, 2005; Heldt and Ressler, 2007), and $GABA_A$ receptor membrane insertion in BLA (Lin *et al*, 2009a, b). Finally, as we have seen, BLA is one of the several sites of extinction-related plasticity; mPFC and hippocampus are engaged as well and may contribute to the expression of extinction memory by modulating amygdalar activity. A major goal of extinction research is to determine how these varied mechanisms interact to produce context- and time-dependent conditioned response suppression.

The literature on extinction of drug- and withdrawal-paired cues is largely silent on AMPA receptor involvement, with the exception of two studies on Narp, which is a protein that binds to AMPA receptors and contributes to their trafficking and clustering at synapses. Both of these studies were conducted in the place conditioning paradigm; the major findings were that Narp knockout mice show delayed extinction of morphine conditioned place preference (Crombag *et al*, 2009) and enhanced extinction of morphine withdrawal-induced conditioned place aversion (Reti *et al*, 2008). It is not immediately obvious how to interpret these findings, both because the knockout was constitutive rather than localized and because so little is known about the neurobiological underpinnings of these two types of extinction, which likely rely on somewhat different substrates. However, at the very least, the data suggest that AMPA receptors have an important role in the extinction of drug- and withdrawal-paired cues, just as they do in fear extinction (also see Sutton *et al*, 2003). In addition to these studies, there is a recent report that GluR2 expression and AMPA/NMDA current ratios were decreased in mPFC in rats that had been re-exposed to a heroin-associated cue in the IVSA paradigm after extinction of

lever pressing (Van den Oever *et al*, 2008). Although the authors of this study suggest that these changes are associated with cue-induced reinstatement of drug-seeking behavior, an alternative explanation is that the changes are reflective of extinction of the response-reinstating value of the cues over the course of the test session.

METABOTROPIC GLUTAMATE RECEPTORS

Metabotropic glutamate receptors (mGluRs) are G protein-coupled receptors mediating slow synaptic transmission. There are eight subtypes, denoted mGluR1–8, which are classified into three groups based on sequence similarity and signal transduction mechanisms: group I (mGluR1, mGluR5); group II (mGluR2, mGluR3); and group III (mGluR4, mGluR6-8). They are located throughout the brain, with different subtypes having different regional and developmental patterns of expression. Some subtypes (eg, mGluR5) have been implicated in learning and memory and experience-dependent forms of synaptic plasticity (Simonyi *et al*, 2005).

Studies on the contribution of mGluRs to extinction have appeared relatively recently, and the literature at this time is somewhat limited (Table 4). Thus far, there are data regarding the role of mGluR1, mGluR5, and mGluR7.

Localized infusions of the mGluR1 antagonist CPCCOEt into BLA before extinction training dose-dependently impair within-session extinction and subsequent extinction retention when extinction training occurs 48 h after acquisition, but not 1 h after acquisition (Kim *et al*, 2007b). The apparent time-dependent nature of mGluR1 involvement is consistent with evidence from other sources that the mechanisms of short- and long-interval extinction may differ (Cain *et al*, 2005; Mao *et al*, 2006; Maren and Chang, 2006; Myers *et al*, 2006). In an electrophysiological study, Kim *et al* (2007a) found that CPCCOEt blocks *ex vivo* induction of synaptic depotentiation in BLA in slices obtained from fear-conditioned animals, whereas the group I mGluR agonist DHPG induces depotentiation in these slices (also see Hong *et al*, 2009). These findings may be consistent with those described in the 'AMPA receptors' section suggesting that BLA depotentiation is a mechanism of extinction, at least under some circumstances.

Both mGluR5 knockout mice (Xu *et al*, 2009) and mGluR7 knockout mice (Callaerts-Vegh *et al*, 2006; Goddyn *et al*, 2008) show deficits in fear extinction. Conversely, systemic administration of the newly synthesized mGluR7 agonist AMN082 before extinction training dose-dependently facilitates fear extinction (Fendt *et al*, 2008). AMN082 has no effect when administered in the absence of extinction training (Fendt *et al*, 2008).

Extinction of conditioned responses to drug-paired cues is sensitive to manipulations of mGluR function as well, as indicated by the finding that systemic administration of CDPPB, a positive allosteric modulator of mGluR5, before extinction training dose-dependently facilitates extinction of cocaine conditioned place preference (Gass and Olive, 2009). This effect was blocked by coadministration of the mGluR5 antagonist MTEP or the NMDA receptor antagonist MK-801, highlighting the functional interactions between mGluRs and NMDA receptors.

TARGETING GLUTAMATE CLINICALLY: CLINICAL USE OF DCS

The finding that DCS can facilitate fear extinction in animals (Walker *et al*, 2002) sparked interest in the idea that this drug might also be effective in facilitating exposure therapy for fear and anxiety disorders in people. DCS has been FDA-approved for some time as an antibiotic treatment for tuberculosis at high doses, allowing for clinical studies examining the utility of this compound in humans to be set up relatively quickly and easily.

The first of the DCS clinical studies (Ressler *et al*, 2004) examined the ability of DCS to enhance exposure therapy for acrophobia, or fear of heights, using virtual reality exposure (VRE) therapy. Previous work had shown improvements in acrophobia outcome measures after 7 weekly VRE therapy sessions (Rothbaum *et al*, 1995). Volunteer participants who met DSM-IV criteria for acrophobia were assigned randomly to groups receiving placebo or one of two doses of DCS (50 or 500 mg) in conjunction with VRE. Participants underwent a suboptimal amount of exposure therapy for acrophobia (two VRE sessions) and were instructed to take a single dose of study medication 2–4 h before each session. Similar to rats in the preclinical work, participants receiving either dose of DCS exhibited significantly more improvement than did those receiving placebo, with no statistical difference between the two doses. DCS-treated patients exhibited less fear and fewer skin conductance fluctuations in the VR environment, lower overall acrophobia symptoms, increased self-reports of exposure to heights in the 'real world,' and higher self-ratings of improvement.

Since then, other groups have found that DCS enhances exposure therapy for other fear and anxiety disorders, including social anxiety disorder (Guastella *et al*, 2008; Hofmann *et al*, 2006), obsessive-compulsive disorder (Kushner *et al*, 2007; Wilhelm *et al*, 2008; but see Storch *et al*, 2007), and panic disorder (Otto *et al*, 2010), indicating that the DCS effect is a relatively general one. The failure in Storch *et al* (2007) may have resulted from administering DCS 4 h before exposure therapy, which may have been too early. There has been one report of a failure of DCS to facilitate exposure therapy for subclinical spider phobia (Guastella *et al*, 2007a) and failures of DCS to facilitate extinction of Pavlovian-conditioned fear in a laboratory situation in humans (Guastella *et al*, 2007b; Grillon, 2009). However, these negative effects may indicate that DCS is useful only in people with clinically significant, maladaptive fear—consistent, perhaps, with the preclinical data suggesting that DCS is particularly effective in stressed animals

(described in the 'Positive modulation of NMDA receptor function' section).

A very recent study examined the utility of DCS as an adjunct to exposure therapy for nicotine addiction in cigarette smokers (Santa Ana *et al*, 2009). Smokers underwent two sessions of smoking cue exposure involving handling cigarettes, lighters, and ashtrays, during which skin conductance responses (SCRs) and self-reports of craving were recorded. One hour before each exposure session, participants were administered 50 mg DCS ($n = 12$) or placebo ($n = 13$). In general, exposure therapy for addiction has not been met with great success, for reasons that remain unclear (Conklin and Tiffany, 2002), and consistent with this, participants in the smoking study who received placebo showed little evidence of extinction of SCR or craving during exposure sessions. Intriguingly, however, participants who received DCS showed facilitated within-session extinction of both measures.

Another recent study examined the effect of DCS on extinction of cocaine cue-induced craving in addicts, using a design similar to that of the smoking cue study in that it involved two sessions in which participants handled paraphernalia and simulated cocaine (Price *et al*, 2009). Two hours before each session, participants received 50 mg DCS ($n = 5$) or placebo ($n = 5$). One week later, a follow-up session was conducted without previous administration of DCS or placebo. Although not statistically significant, there was a trend in follow-up toward decreased self-reported craving in the DCS group relative to that in the placebo group. Owing to the small group sizes, these results are preliminary, but they are suggestive of a facilitation of extinction of cocaine cue-induced craving by DCS. However, DCS also significantly enhanced drug craving during exposure sessions, leading the authors of this study to question the clinical utility of DCS in the treatment of cocaine addiction.

There are two other potential problems with the clinical use of DCS that have emerged in the preclinical (animal) literature, and which need to be considered alongside the successes. One is the finding (discussed earlier) that DCS facilitates extinction but not re-extinction of a conditioned fear response (Langton and Richardson, 2008). Together with related findings that the mechanisms of re-extinction differ under some circumstances from those of original extinction (Chan and McNally, 2009; Laurent *et al*, 2008; Laurent and Westbrook, 2008), this finding may imply that DCS will be less effective as a clinical tool in patients who have relapsed after treatment and are seeking treatment again. Relapse is prevalent in both anxiety disorders and addiction; hence, it will be important to determine whether DCS is useful with this population and, if necessary, to develop alternative approaches. A second potential cause for concern is the finding that DCS modulates not only extinction but also reconsolidation (Lee *et al*, 2006, 2009). Reconsolidation is a form of memory consolidation that occurs after reactivation of a memory formed previously. For example, after training a rat to associate a tone with a foot shock, briefly re-exposing the rat to the tone seems to make the previously consolidated memory sensitive to disruption once again, such that the rat will be amnestic with regard to the tone when tested some time later if it was administered a memory-impairing treatment at the time of memory reactivation (Nader *et al*, 2000). Perhaps consistent with its function as a cognitive enhancer, DCS has the opposite effect; that is, it potentiates memory reconsolidation when administered in conjunction with a brief re-exposure to a previously conditioned stimulus, such that rats exhibit stronger memories when tested later. This is true for both fear conditioned stimuli (Lee *et al*, 2006) and drug-related conditioned stimuli (Lee *et al*, 2009). Reconsolidation and extinction are highly related phenomena, being distinguished procedurally by the duration of CS re-exposure, such that short re-exposures seem to promote reconsolidation and long re-exposures promote extinction (Eisenberg *et al*, 2003; Pedreira and Maldonado, 2003; Suzuki *et al*, 2004). This suggests that there may be a danger in using DCS clinically if an exposure therapy session is too brief or otherwise favors memory reconsolidation as opposed to extinction. At present, there are no data by which to assess the impact of these two potential problems in clinical populations, but they will be important considerations if DCS is to advance from being an experimental drug to being accepted and used as a clinical tool.

FUTURE RESEARCH DIRECTIONS

A great deal has been learned about the contribution of glutamate to extinction, but there is still much more work to be done. An unanswered question in the fear extinction literature, in particular, is how the apparently multiple mechanisms underlying extinction interact. Focusing just on BLA, a priority in future research will be identifying the various forms of synaptic plasticity involved, keeping in mind that different ones are likely to occur in different cell types, and that the nature of that plasticity might change depending on the circumstances of extinction training—for example, whether extinction is occurring for the first or second time, or if the interval between acquisition and extinction training is long or short.

The literature on extinction of conditioned drug craving and withdrawal is still in its infancy, but interest in this area is increasing and progress is being made. Immediate, major goals of this work include developing a map of the underlying circuitries and characterizing the interactions among the structures that are involved. It is likely that this type of extinction involves similar cortico-limbic mechanisms as implicated in fear extinction (Myers and Carlezon, 2010b), but more evidence is required to solidify that view. Having done this, teasing apart the contribution of glutamate receptor subtypes to the encoding, consolidation, and expression of drug-related extinction memory will be more feasible.

Clinical Implications

Basic research on glutamate receptor involvement in extinction has had an immediate, direct clinical benefit in the use of DCS to facilitate exposure therapy for fear and anxiety disorders. Particularly in the context of addiction, however, more study is required to determine the generality of the DCS effect. The evidence for clinical efficacy of DCS in exposure therapy for nicotine and cocaine addiction (Price *et al*, 2009; Santa Ana *et al*, 2009) is encouraging, and this, together with the growing animal literature on DCS-induced facilitation of extinction of conditioned drug craving and withdrawal (described in the 'Positive modulation of NMDA receptor function' section), provides a rationale for further study.

DCS is not the only drug that facilitates extinction. We have described three others that do as well: the AMPA receptor agonist PEPA, and the mGluR agonists AMN082 and CDPPB. Any of these might be an attractive candidate for further development as a potential clinical tool, assuming that they do not have unintended side effects. In this respect, the indirect, modulatory effect of DCS on glutamate function might be the key to its putative safety and efficacy.

Looking further ahead, if our understanding of glutamate actions within specific cell populations or brain regions were increased, technology might evolve to permit targeting treatments to those substrates to facilitate and maximize the generalizability of extinction. For example, gene therapy might become available whereby genes encoding NMDA receptor subunits could be delivered specifically to the amygdala or mPFC, before exposure therapy.

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DISCLOSURE

Karyn M Myers: I declare that, except for income received from my primary employer, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest. *William A Carlezon, Jr.*: I have US patents related to the use of kappa-opioid receptor ligands in the treatment of psychiatric disorders (Assignee: McLean Hospital). In the past 3 years, I have received compensation for professional services from The American College of Neuropsychopharmacology, Huya Bioscience International, Infinity Pharmaceuticals, Lantheus Medical Imaging, The Society for Neuroscience, and Transcept Pharmaceuticals. *Michael Davis*: The current paper will discuss an off-label use of D-cycloserine as an adjunct to psychotherapy. I have US patents for the use of D-cycloserine as an adjunct to psychotherapy and the use of D-cycloserine to be administered before sleep on the day on which psychotherapy occurs. I am a partner in a company called Therapade and another called Extinction Pharmaceuticals. Extinction Pharmaceuticals will try to license this technology to commercialize the use of D-cycloserine as an adjunct to psychotherapy. Should this occur, I would receive a signing fee and certain milestone payments over the next several years, during which I expect each payment will be more than $10 000. Once the indication is approved by the FDA, I am entitled to royalties which could exceed $10 000 per year. During the past 3 years, I have received research support, an unrestricted gift, and an honorarium from Astra-Zeneca Pharmaceuticals.

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