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Serotonergic Mechanisms in Addiction-Related Memories

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Abstract

Drug-associated memories are a hallmark of addiction and a contributing factor in the continued use and relapse to drugs of abuse. Repeated association of drugs of abuse with conditioned stimuli leads to long-lasting behavioral responses that reflect reward-controlled learning and participate in the establishment of addiction. A greater understanding of the mechanisms underlying the formation and retrieval of drug-associated memories may shed light on potential therapeutic approaches to effectively intervene with drug use-associated memory. There is evidence to support the involvement of serotonin (5-HT) neurotransmission in learning and memory formation through the families of the 5-HT_1 receptor (5-HT_1R) and 5-HT_2R which have also been shown to play a modulatory role in the behavioral effects induced by many psychostimulants. While there is a paucity of studies examining the effects of selective 5-HT_{1A}R ligands, the available dataset suggests that 5-HT_{1B}R agonists may inhibit retrieval of cocaine-associated memories. The 5-HT_{2A}R and 5-HT_{2C}R appear to be integral in the strong conditioned associations made between cocaine and environmental cues with 5-HT_{2A}R antagonists and 5-HT_{2C}R agonists possessing potency in blocking retrieval of cocaine-associated memories following cocaine self-administration procedures. The complex anatomical connectivity between 5-HT neurons and other neuronal phenotypes in limbic-corticostriatal brain structures, the heterogeneity of 5-HT receptors (5-HT_XR) and the conflicting results of behavioral experiments which employ non-specific 5-HT_XR ligands contribute to the complexity of interpreting the involvement of 5-HT systems in addictive-related memory processes. This review briefly traces the history of 5-HT involvement in retrieval of drug-cue associations and future targets of serotonergic manipulation that may reduce the impact that drug cues have on addictive behavior and relapse.

Keywords

Serotonin receptors; cocaine; self-administration; memory retrieval; extinction; conditioned stimuli

Introduction

The abuse of alcohol, nicotine and illicit drugs comprises a global dilemma, marked by considerable morbidity and mortality [320]. Initial drug use typically occurs as a component of exploration, novelty or pleasure-seeking during adolescence [159,180], with a subpopulation of drug users exhibiting vulnerability to the transition from abuse to “addiction” [330]. Addiction is defined here as a chronic disorder characterized by persistent drug-seeking, which

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has been modeled extensively in animals in self-administration studies (Fig. 1) [169,335]. The incentive-motivational state focused on drug use seen in addiction appears to be fuelled by impaired neurobiology and reorganization of brain circuits. Affected brain circuits include motivational systems in the hypothalamus and brainstem and their reciprocal links with higher order limbic-corticostriatal structures involved in the complex cognitive, emotional and associative abilities of the brain [307]. Cortical regions, such as the prefrontal cortex and their associated circuits appear to be particularly sensitive to plasticity incurred due to repeated pairing of environmental stimuli (*e.g.*, drug paraphernalia, people and places associated with drug use, *etc).* with exposure to abused drugs [14,116]. These associations between environmental cues and the drug-taking experience become well consolidated into memory [118,182] and imaging studies have verified that re-exposure to drug-related stimuli activate attention and memory circuits [69,116,236,326]. Drug-associated memories can trigger conditioned emotional responses in addicts [238] and "craving" (desire for drug) [22,109, 121,162] which is often cited by individuals to explain their relapse [127,269].

The process of association between the drug and experiential aspects of drug abuse is driven by Pavlovian (classical) learning [238] and there is a growing recognition and interest in understanding the biological and behavioral mechanisms underlying the encoding of drug-related memories. This interest is sensibly rooted in the fact that recovery is punctuated with remissions and relapses [205,237,300], and efficacious means to extend abstinence are needed. If addiction is a "disease of learning and memory" as recently proposed [138,326], then therapeutic gains may be achievable with a more complete understanding of the neurobiology of drug-related memories. The potential success of such approaches is suggested by observations that pharmacological manipulations can impair responsivity to drug-associated conditioned cues in humans [250,263,299] and animals [61,181,292].

Learning occurs during the three general phases of acquisition (initial learning), consolidation (molecular stabilization of long-term memory) and retrieval (recall of initial learning) [32, 80,142,178]. The formation of memory is dependent upon dynamic changes in synaptic plasticity, an important neurochemical process through which protein modifications and/or synthesis result in altered synaptic strength (for comprehensive review, [141,148,176,202]). Two cellular models of the molecular mechanisms that underlie synaptic changes during learning and memory are long-term potentiation (LTP) and long-term depression (LTD) (for reviews, [175,196,199]). Activity-dependent modifications of *N*-methyl-D-aspartate receptors (NMDAR) and α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptors (AMPAR) in the postsynaptic neuron are well described mechanisms of these forms of neuroplasticity (for reviews, [59,77,179]). The most extensively studied mammalian form of synaptic plasticity is NMDAR–dependent LTP in hippocampal neurons [18]. In this situation, strong synaptic stimuli lead to a transient activation of NMDAR in dendritic spines and increased calcium released from endoplasmic reticulum resulting in the activation of multiple signaling cascades. Two key protein kinases within this pathway are calcium/calmodulin-dependent kinase type II (CaMKII) and cAMP-dependent protein kinase A (PKA) [21,90,193,333], both of which catalyze the phosphorylation and synaptic insertion of AMPARs into the PSD [52,65,129, 192,195,251,295]. A strengthening of synaptic plasticity is subsequently achieved by stimulation of gene transcription and protein synthesis via the activation of several other downstream effectors including protein kinase C (PKC), Ras-guanosine triphosphatase activating protein (Ras-GTPase), extracellular signal-regulated protein kinase (ERK), p38 mitogen-activated protein kinase (p38 MAPK) and numerous PSD proteins [24,89,113,122, 163,173,308,332,336]. The molecular mechanisms underlying LTP and hence synaptic plasticity are now viewed to be mechanistically important in the plasticity underlying the maladaptive reward learning which occurs following stimulant administration [146,153,319, 334].

Glutamatergic systems critical to synaptic plasticity are under important modulatory control afforded by other neurotransmitter systems including monoaminergic neurotransmission [93, 191,265,293]. Dopamine (DA) through actions at the D_1R, in particular, facilitates LTP via alterations in AMPAR trafficking [108,143,334] and continues to be an important candidate in reward learning and long-term plasticity in addiction [59,139,146,153,155]. Serotonin also clearly modulates glutamatergic-encoded neuroplasticity [297,324], an observation which was made at the dawn of Kandel's studies of synaptic plasticity underlying the simple classical conditioning of the gill-withdrawal reflex in *Aplysia* [33]. Receptors linked to adenylyl cyclase (AC) signaling are important mediators of this plasticity observed in *Aplysia* [11,60,125]. Of the 16 subtypes of 5-HT receptors (5-HT_XRs), several couple to AC (5-HT_1R, 5-HT_4R, 5-HT_6R and 5-HT_7R), the 5-HT_2R family couples to inositol phosphate signaling whereas the 5-HT_3R is a ligand gated ion channel [20,96,134,164,235,262].

Serotonin signaling through several of these receptors may contribute to neural plasticity that underlies the encoding of drug associated memories. As a component of the complex processes that underlie the neurobiology of addiction, a greater understanding of serotonergic mechanisms in this aspect of addictive processes (Fig. 1) may open new doors to enhance recovery. Therapeutic gains have been reported in the treatment of alcoholism, smoking and illicit drug addictions with selective serotonin reuptake inhibitors (SSRIs) under certain conditions (*e.g.*, [2,87,137,185,270,289,309,325]). Serotonergic manipulations may also prove therapeutic in psychostimulant addiction, which poses a particularly difficult public health problem due to the limited treatment options and extenuating ramifications for the individual user and society [133,165,220,296]. In the present review, we focus on the body of knowledge developed to suggest that 5-HT plays a role in stimulant-associated memories and the underlying synaptic plasticity. As the most complete information is available for the *Erythroxylum coca* alkaloid cocaine, we focus on this abused psychostimulant. A greater understanding of serotonergic mechanisms underlying the conditioned association between the cocaine exposure and environmental stimuli will provide new ideas for innovative approaches to treatment in addiction.

Cocaine

Cocaine use remains a significant public health problem across the globe [320]. Upwards of 15% of cocaine users are ultimately diagnosed with addiction [303,330], and recovery success is limited with a high degree of recidivism [91,303]. While behavioral and cognitive therapies can provide alternative treatment approaches, no proven effective and accessible medications for the treatment of this detrimental form of abuse and addiction have been validated despite an intense focus on their development [28,144,145,174,230,257,301].

Cocaine potently binds to the 5-HT transporter (SERT) to inhibit reuptake of 5-HT and increase efflux into the synapse [166] in addition to its extensively characterized ability to inhibit catecholamine reuptake [5,101,264]. Serotonergic manipulations (e.g., 5-HT precursors, neurotoxins, 5-HT agonists and antagonists) interfere with expression of the behavioral effects of cocaine (for review, [34,131,222,223,331]) while the neurochemical consequences of repeated cocaine exposure include altered expression of 5-HT transporters and receptor subtypes in both animals [10,67,240] and humans [189,245]. To date, much of the research which has examined the effects of serotonergic ligands on the behavioral effects of cocaine in animals has centered on the 5-HT_1R and 5-HT_2R subtypes [34,222], thus the role of these receptors in cocaine-associated memories will be the main focal objective for discussion in this review.

The 5-HT_1R family forms the largest class of 5-HT_XR subtypes and is comprised of the 5-HT_{1A}R, 5-HT_{1B}R, 5-HT_{1D}R, 5-HT_{1E}R and 5-HT_{1F}R subtypes [177]. This receptor family

couples to Gi/o proteins to preferentially inhibit cyclic adenosine monophosphate (cAMP) formation, although linkage to other signaling effectors has also been demonstrated (*e.g.*, phosphatidylinositol pathway and PKC [20,262]). The 5-HT_{1A}R and 5-HT_{1B}R have received considerable attention in preclinical studies. For example, the stimulation of the 5-HT_{1A}R [employing 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) and/or buspirone] reduced cocaine-evoked hyperactivity [48,258] (although see, [222]) and lever responding for cocaine in the rat self-administration model (see, Models for the Study of Cocaine-Associated Memories) [132,222,248]. Conversely, 5-HT_{1B}R agonists enhanced cocaine-induced hyperactivity [260] and the reinforcing effects of cocaine inferred from an increase in lever responding for cocaine as measured in the self-administration paradigm [243,244,259]. However, studies with 5-HT_{1B}R knockout (KO) mice found an increased propensity to self-administer cocaine, an effect which may indicate a decrease in the reinforcing effects of the psychostimulant [53,268]. A possible rationale for such differences comes from the increasing evidence that KO mice undergo important compensatory changes in other 5-HT_XR subtypes and/or neurotransmitter systems during development [111,294] which may be implicated in observed behavioral effects in KO mouse models.

The 5-HT_2R family (5-HT_{2A}R, 5-HT_{2B}R and 5-HT_{2C}R) is linked preferentially to $G_{q/11}$ and activation of these receptors increases the hydrolysis of inositol phosphates and elevates cytosolic calcium [134,164,186,262]. Due to the limited distribution of the 5-HT_{2B}R subtype in brain and lack of availability of selective 5-HT_{2B}R ligands [83], the 5-HT_{2A}R and 5-HT_{2C}R are the most extensively researched subtypes of this family in addiction and memory formation processes [34,209]. Pretreatment with selective 5-HT_{2A}R or 5-HT_{2C}R ligands presents a relatively consistent pattern of effects on cocaine-induced behaviors in rodents (for review, [34]). An acute systemic injection of selective 5-HT_{2A}R antagonists or 5-HT_{2C}R agonists blocked, while 5-HT_{2A}R agonists or 5-HT_{2C}R antagonists enhanced, the hypermotive effects of cocaine at doses of the ligands that did not modify basal behavior [98,200,203]. Additionally, rates of responding for cocaine in a self-administration task is suppressed by a selective 5-HT_{2C}R agonist and enhanced by a selective 5-HT_{2C}R antagonist [98,99,120] suggesting an important role for the 5-HT_{2C}R in control of the overt reinforcing effects of cocaine. In contrast, selective 5-HT_{2A}R antagonists have no effects on rates of responding for cocaine in a self-administration task [97,98,233]. Based upon this partial dataset, once the 5-HT_1R and 5-HT_2R subtypes can be distinguished pharmacologically from one another, their influences include an excitatory role for the 5-HT_{1B}R and 5-HT_{2A}R and an inhibitory role for the 5-HT_{1A}R and 5-HT_{2C}R in the control of cocaine-induced behaviors.

Models for the Study of Cocaine-Associated Memories

The impact of cocaine on 5-HT systems coupled with the influence of 5-HT in the molecular cascade of events in the encoding of memories (see, Serotonin Mechanisms in Memory Formation) [148] supports a role for 5-HT neurotransmission in the processes through which cocaine-associated memories evolve [140,153,172,267]. These assessments of drug-associated memories have employed several different animal models [88,103,112,190,215,276,278, 316]. The assay with the greatest construct validity, but also the most complex to dissect with regard to memory processes, is the drug self-administration procedure [15,88,110,124,266]. Cocaine self-administration models in animals have been adapted to explore drug-associated memories and the long-term consequences of cocaine intake in the laboratory. In one of its common variant in rodents, intravenous catheters are surgically implanted and subjects are allowed to complete an operant response (e.g., lever press, nose poke) to deliver a bolus injection of cocaine [110,147,291]. During the acquisition of a cocaine self-administration (Fig. 2), the learning paradigm promotes the establishment of a linkage between the cocaine-taking contextual (diffuse) cues, experimenter-delivered salient (discrete) environmental cues paired with the cocaine delivery, and the reinforcing and interoceptive effects of cocaine. In

the language of classical conditioning, the effects of cocaine can be considered as an unconditioned stimulus (US). Repeated pairing of the US with the environmental context (*e.g.*, the physical characteristics of the environment in which the drug is consumed including the presence of the houselights, levers, *etc*.) and discrete cues simultaneously delivered with cocaine (*e.g.*, stimulus lights, tones, sound of drug delivery apparatus), a learned association between the conditioned stimuli (CS) and US (CS-US) is acquired. Thus, the CS complex is comprised of contextual and discrete cues. Following the training phase, the animals are subjected to an imposed withdrawal period (forced abstinence; [107,119,242]) or undergo extinction to the contingencies of the paradigm [99,152,286,288,291,292]. Following acquisition and either forced abstinence or extinction, retrieval of the conditioned association is assessed upon re-exposure to the CS complex and is implied by the behavioral output (*e.g.*, lever press) in the absence of actual cocaine delivery ("drug-seeking") [75,291]. The magnitude of operant responses on the previously drug-paired operandum can then be quantified as a measure of drug-seeking behavior supported by the CS complex [288]. Termed "cue-evoked reinstatement", the behavioral output upon re-exposure to cocaine-associated cues shares aspects of construct and predictive validity to the human experience of relapse in the face of environmental triggers such as handling drug paraphernalia [58,68,238,327].

The cue-elicited reinstatement paradigm employed as a component of self-administration studies normally involves extensive extinction training. This procedure typically involves repeated presentation of the diffuse contextual cues, but not the discrete CS cues, in the absence of the US (cocaine infusions) [66,94,287,288,291] to weaken the association between the behavior (*e.g.*, lever press, nose poke) and the delivery of the primary reinforcer (drug) but maintain the incentive motivational value of the discrete cues [88,152,246,286,288,291,292]. Occasionally, the ability of the diffuse cues to elicit reinstatement has been examined, wherein extinction occurs in a different context (Context B) to that of the self-administration and cue-elicited reinstatement phases (Context A; [23,66,99,154,201]). In these paradigms, extinction is not a case of "forgetting," but rather an active learning process that occludes, but does not "erase," previously learned behaviors [26,86,247,261,306]. Thus, the previously established CS-US association is not eliminated but rather suppressed by new learning, which has been described as a "CS-no US" association [25,246]. Upon re-exposure to the discrete CS complex following extinction training, retrieval of the original memory (CS-US) or retrieval of the newly formed extinction memory (CS-no US) may result [44,160,224]. Reduction of lever responding in the presence of the CS complex via pharmacological manipulation is viewed as a disruption of the retrieval of cocaine-associated memories for cocaine-paired stimuli.

The remainder of the present assessment will elucidate the probable role for 5-HT actions at its receptors in the mechanisms underlying the retrieval of cocaine-associated memories (drug-seeking behavior) and suggest how 5-HT manipulations might prove useful in therapeutic approaches to suppress relapse in human cocaine addicts.

Serotonin Mechanisms in Memory Formation

The involvement of 5-HT in memory processing is not surprising given the fact that serotonergic pathways provide significant innervation to cortical and subcortical structures known to be involved in cognition from their parent neurons of origin in theraphe nuclei [7]. However, results from human and animal studies have yielded inconsistent findings concerning the directionality of its role. This situation reflects the complex nature of serotonergic processing of information in brain, the lack of available selective molecular and pharmacological tools as well as the need to evaluate the question at multiple levels of memory systems [211,318]. Some protocols have evaluated the impact of 5-HT_1R and 5-HT_2R ligands administered either before the learning session or after the learning session to tap into the acquisition and consolidation phases of memory, respectively [207,208], while only a handful

of studies have specifically examined the role of these 5-HT_XR in memory retrieval tasks. As return to cocaine use is often linked with retrieval of drug-associated memories (see Introduction), we will only review data employing tasks that tap into this aspect of memory-related behavior as most analogous to models employed to study cocaine-associated memories (see Models for the Study of Cocaine-Associated Memories).

There is experimental evidence that 5-HT_{1A}R and 5-HT_{1B}R signaling are involved in acquisition and retrieval of learning while the specific involvement of this receptor in consolidation of learning has not been extensively addressed. Pre-training administration of a 5-HT_{1A}R agonist [*e.g.*, flesinoxan, buspirone or 8-OH-DPAT] enhanced **acquisition** of new learning [35,63,208] in behavioral tasks associated with appetitive motivation, such as the delayed-matching-to-position or delayed nonmatch-to-sample tasks, whereas administration of the agonist impaired retention of new learning in spatial memory tasks [16,167]. In addition, administration of 8-OH-DPAT following the acquisition session (2hr) hindered consolidation of the new learning [167]. Interestingly, pretreatment with a 5-HT_{1A}R agonist impaired **retrieval** of spatial and contextual cues in passive avoidance paradigms and the Morris water maze [6,49,51,150,188,188,218,221,253,284,311], an effect linked to stimulation of the postsynaptic, as opposed to the presynaptic, 5-HT_{1A}R [49,241]. Contradictorily, one study reported an improvement in memory retrieval after pretreatment with a 5-HT_{1A}R antagonist in the object recognition task [252], however, this observation has not been replicated in other paradigms of memory retrieval [210,212]. The 5-HT_{1A}R may act in consort with glutamate systems to regulate memory processes as a 5-HT_{1A}R antagonist reversed impairment of **retrieval** evoked by the NMDAR antagonist MK 801 in object recognition and radial arm maze tasks [19,50,252]. Pretraining administration of a 5-HT_{1B}R antagonist enhanced **acquisition** of learning in an autoshaping task [213] while post-training administration of a preferential 5-HT_{1B}R agonist impaired **consolidation** of learning in this same task [212]. Thus, while difficult to tease apart based upon the incomplete dataset, there is experimental evidence to suggest that the 5-HT_{1A}R and 5-HT_{1B}R play differential roles in phases of memory.

The 5-HT_2R signaling pathway [186,262] is a serotonergic target of interest in understanding the acquisition and consolidation of learned behaviors and, to a lesser extent, the retrieval of memories engendered in associative-learning memory models (*e.g.*, autoshaping tasks [206, 207,256]). To date, only non-selective ligands have been employed to investigate the role of the 5-HT_{2A}R and 5-HT_{2C}R subtype in memory retrieval paradigms with predictably conflicting results (see Cocaine). The 5-$HT_{2A/2C}$R antagonists (*e.g.*, such as methysergide and mesulergine) investigated to date have been reported to interfere with memory retrieval in tasks involving recall of visual cues in a delayed non-match to sample task [197], although opposite effects have been reported in auditory and radial arm maze memory tasks [13,274,275].

The interpretation of these discrepant data must take into account the nature and degree of difficulty of the paradigms employed, the selectivity of the ligands and doses used (*e.g.*, 8-OH-DPAT possesses affinity for both the 5-HT_{1A}R and 5-HT_7R [126]), the neural circuit involved (*e.g.*, hippocampus *versus* prefrontal cortex), the synaptic localization (*e.g.*, whether pre- versus postsynaptic 5-HT_XR are manipulated), the developmental stage and age of animals at time of testing (*e.g.*, adolescent *versus* adult), the extent of training (*e.g.*, one trial *versus* multiple trials) and the timing of the administration of the ligands (*i.e.*, injection before or after training session or retrieval test, *etc.*). These factors taken in conjunction with a comparative assessment of selective 5-HT_XR ligands and doses across several behavioral tasks are required to clarify the role of 5-HT_1R and 5-HT_2R in memory retrieval processes. However, from a general consideration of the present collection of studies, the stimulation of postsynaptic 5-HT_{1A}R and blockade of 5-$HT_{2A/2C}$R may interfere with memory retrieval processes, and thus serve as potential candidates in altering recall of cocaine-associated memories.

Serotonin and Cocaine-Associated Memories

The involvement of individual 5-HT_XR and transduction systems in mediating cocaine-associated memories requires further exploration with a goal to uncover which serotonergic manipulations might promise translation to the clinic as effective adjuncts to therapy in cocaine addiction. The clinical human psychopharmacology research with selective 5-HT_XR ligands is truly limited due to the paucity of selective pharmacological compounds available for use in humans [74,117,272,280]. Of the pharmacological manipulations assessed in humans to date, increases in serotonergic tone via administration of the 5-HT transporter substrate fenfluramine were shown to reduce cocaine craving in human cocaine-dependent subjects [39–41,255]. Preclinical studies have also illustrated that the re-exposure to cocaine-associated cues [29,47] or even to other reward-associated cues [214] results in significant alterations of 5-HT efflux in the prefrontal cortex suggesting that retrieval of cocaine-associated memories involves cortical 5-HT function. Paradoxically, pharmacological manipulations that either decrease (*e.g.*, administration of the neurotoxin 5,7-dihydroxytryptamine) or increase extracellular 5-HT (*e.g.*, administration of a SSRI) prior to exposure to the CS complex in a reinstatement session reduced behavioral responding elicited by cues previously associated with cocaine in rats [9,38,312,313]. In the remainder of this article, we will review the handful of published observations in support of the role of 5-HT substrates in the processes involved in the retrieval of cocaine-associated memories.

Cocaine-Associated Memories and 5-HT_1R

The 5-HT_{1A}R agonist impairs the memory retrieval of spatial and contextual cues (see Serotonin Mechanisms in Memory Formation) thus the prediction is that 5-HT_{1A}R agonist would also block retrieval of cocaine-associated memories. To date, a selective 5-HT_{1A}R agonist at doses that act at either pre- or postsynaptic 5-HT_{1A}R has not been assessed in reinstatement sessions. However, following acquisition of cocaine self-administration and subsequent extinction of the operant response, acute administration of the 5-HT_{1A}R antagonist WAY 100635 30 min prior to test did not alter cue-induced reinstatement [37]. Thus with only a limited amount of data the role of 5-HT_{1A}R in retrieval of cocaine-associated memories remains unclear.

There is a paucity of studies determining the role of the 5-HT_{1B}R in memory retrieval as noted, however, 5-HT_{1B}R agonists are reported to potentiate the reinforcing effects of cocaine. Thus, one might expect a 5-HT_{1B}R agonist to enhance retrieval of cocaine-associated memories. However, acute administration of the 5-$HT_{1B/1A}$R agonist RU24969 15 min prior to test reduced retrieval of cocaine-associated memories following extinction [1]. The effects of RU24969 were deemed to be mediated by 5-HT_{1B}R stimulation as administration of the selective 5-HT_{1B}R antagonist GR127935 reversed the effects of RU24969 on cocaine-associated memories; the antagonist alone had no effect [1]. The differential control afforded by 5-HT_{1B}R agonists over the behavioral consequences of exposure to cocaine-associated cues *versus* the reinforcing effects of cocaine may be consistent with dissociable neural mechanisms suggested to underlie the reinforcing effects of a psychoactive drug *versus* conditioned effects of the drug [54,92,204]. Similar to the effects observed with cocaine-associated cues, the 5-HT_{1B}R agonist also reduced the level of responding elicited with sucrose-associated cues [1]. As the administration of this ligand at the chosen doses did not affect spontaneous locomotor behavior (and assuming that RU24969 did not alter perceptual processes significantly), the authors concluded that RU24969 elicited a general decrease in motivation for appetitive stimuli (see below for further discussion) [1]. While further studies are required to delineate the exact role of 5-HT_{1A}R and 5-HT_{1B}R in retrieval of cocaine-associated memories, the limited dataset presented so far indicate that manipulation of either receptor subtype shows little promise in selectively suppressing the retrieval of cocaine-associated memories.

Cocaine- Associated Memories and 5-HT_{2A}R/5-HT_{2C}R

The 5-HT_2R family is an important serotonergic target of interest in understanding the cellular and behavioral effects of cocaine (see Cocaine [34,222,223]). The results of studies that employed non-selective 5-$HT_{2A/2C}$R antagonists in a handful of memory retrieval studies published to date are conflicting (see Serotonin Mechanisms in Memory Formation). However, a consistent pattern of effects of 5-HT_{2A}R and 5-HT_{2C}R ligands over cocaine-related behaviors as observed (see Cocaine [34]). Based on this research, selective 5-HT_{2A}R antagonists and selective 5-HT_{2C}R agonists might be expected to block the retrieval of cocaine-associated memories.

Early studies that employed less selective 5-$HT_{2A/2C}$R antagonists did not observe changes in retrieval of cocaine-associated memories following extinction training [37,282]. More recent studies indicate that pretreatment with selective 5-HT_{2A}R antagonists potently blocked retrieval of cocaine-associated memories following extinction of operant responding in the absence of discrete cues [97,233]. The administration of M100907, the most selective 5-HT_{2A}R antagonist available to date (volinanserin; [228,233]), effectively reduced retrieval of cocaine-associated memories observed under conditions that minimize the potential for confounds associated with the operant pretraining and the stress of food deprivation [55,123, 323]. This effect does not appear to be related to general behavioral disruption as the same doses of the antagonist did not alter locomotor activity nor retrieval of sucrose-associated memories upon re-exposure to cues previously linked to sucrose self-administration [233]. Pretreatment with either a selective (RO 60-0175) or non-selective (mCPP, MK-212) 5-HT_{2C}R agonist suppressed rates of lever responding on re-exposure to cues previously associated with cocaine self-administration after extinction training [36,99,231; Nic Dhonnchadha and Cunningham, unpublished data]. These suppressive effects were reversed by co-administration of 5-HT_{2C}R antagonists, which alone failed to alter retrieval of cocaine-associated memories, indicating that the inhibition of lever responding upon re-exposure to cues linked to cocaine self-administration are mediated by the 5-HT_{2C}R [36,99,231]. Additionally, the same doses of RO 60-0175 did not alter retrieval of cue-evoked memories in the sucrose self-administration paradigm [36]. In summary, these results point to ligands with selective 5-HT_{2A}R antagonist or 5-HT_{2C}R agonist properties as viable candidates to promote the disruption of retrieval of cocaine-associated memories.

Many studies examining the effects of serotonergic agonists in cue-elicited drug-seeking behavior employed antagonists to primarily verify the selectivity of the agonist. Only one dose of the antagonist is employed in most instances with the dose typically based upon previous experiments indicating a blockade/reversal of an effect of the chosen agonist (*e.g.*, 5-$HT_{1A/1B}$R) [36]. If one were to conduct a complete dose-response curve for the effects of the antagonist alone, a completely different story might be uncovered, e.g., inverse agonist effects. This is an important (as yet unanswered) question with respect to the involvement of the 5-HT_{2A}R and 5-HT_{2C}R in drug-seeking behavior, as a myriad of articles report inverse agonist activity *in vitro* and *in vivo* for the compounds employed as antagonists of these receptor subtypes [207,229,322]. Additionally, there is a growing literature about the tonic vs. phasic nature of 5-HT_{2A}R and 5-HT_{2C}R control in the brain. The 5-HT_{2A}R does not appear to exert tonic influence upon DA neuronal firing or DA release (at least in the regions thus far studied), but stimulation of the 5-HT_{2A}R with an exogenous agonist reveals an enhancement of DA neuronal output which is physiologically significant. The 5-HT_{2C}R, on the other hand, appears to provide both tonic and phasic modulation of DA neurotransmission which is region dependent [34]. With the exception of the 5-HT_{2A}R antagonist M100907 [233], further studies encompassing a wider range of doses of selective 5-HT_{1A}R, 5-HT_{1B}R and 5-HT_{2C}R antagonists (as well as agonists and inverse agonists) are required to determine the involvement of these receptor subtypes in the retrieval of cocaine-related memories.

The ability of a 5-HT_{2A}R antagonist or 5-HT_{2C}R agonist to reduce the impact of drug-, but not food-associated, stimuli [36,233] may be related to the fact that neuronal substrates respond differently to drugs *versus* natural rewards and their associated stimuli. Cocaine has been described as "hijacking" the natural learning substrates [157,158,328] and resulting in maladaptive responses to cues previously associated with cocaine self-administration. Repeated exposure to cocaine or other drugs of abuse leads to persistent neural adaptations, such as changes in neuronal morphology as well as protein and gene expression in higher order limbic-corticostriatal structures involved in the complex cognitive, emotional and associative abilities of the brain [307]. These adaptations are thought to render this circuit hypersensitive to drugs and drug-associated stimuli and to play a prominent role in attributing incentive salience to stimuli, that is, the manner in which stimuli are perceived as attractive, causing drugs and drug-associated stimuli to become excessively 'wanted' [78,232,267,322]. Further studies examining the effects of selective serotonergic ligands in animal models of memory formation may aid in deciphering the impact of cocaine administration on normal processing stages [206].

The timing of injections of 5-HT ligands relative to experimental assessment of acquisition, consolidation and retrieval is very important. In the case of most published studies, ligand administration preceded the test for memory retrieval. In this case, several important controls must be considered to allow linkage of observed effects of treatment to disruption of memory recall. To assess the possibilities of performance deficits due to behavioral disruption consequent to the doses of a ligand, simple motility and exploratory patterns are frequently assessed. To measure the specificity of the ligand to affect memories for contextual and discrete cues associated with cocaine *versus* memories for contextual and discrete cues associated with other appetitive reinforcers, the 5-HT_XR ligand manipulation may also be analyzed in a food or sucrose self-administration protocol and reward-seeking assessed in response to cues previously associated with food or sucrose self-administration, respectively. These control experiments for the observed effects of a certain ligand on retrieval of cocaine-associated memory are not ideal and need to be refined. For example, in addition to these performance and reward specificity considerations, a serotonergic pretreatment before memory retrieval tests could result in perceptual deficits that impair recognition of either the contextual or discrete cues of the CS complex. The examination of these ligands in parallel paradigms that do not involve appetitive-linked responses (*e.g.*, spatial cue tasks) may help clarify this issue and refine the ability to interpret observations about retrieval of drug-associated memory in reinstatement self-administration models.

Possible Molecular Mechanisms Underlying the Role of 5-HT in Cocaine-associated Memories

Despite the undeniable support for 5-HT_XR participation in learning and memory processes and evidence to indicate participation in cocaine-associated memories, the potential manner in which 5-HT contributes to the molecular basis for plasticity has been largely absent from discussion of memory formation in mammals. To date, our knowledge is derived from the elegant studies which examined memory storage underlying the gill-withdrawal reflex of *Aplysia* [148]. These studies indicate that memory formation underlying this reflex in *Aplysia* involves presynaptic mechanisms of LTP. In *Aplysia*, 5-HT release subsequent to tail stimulation leads to the activation of AC and a resultant rise in cAMP levels. In turn, cAMP activates PKA, closure of K^+ channels and increased intracellular calcium release, mechanisms believed to contribute to classical conditioning of the gill-withdrawal reflex [11,60,125]. The exact 5-HT_XR involved in the activation of AC involved in memory storage underlying the gill-withdrawal reflex of *Aplysia* by 5-HT remains unclear, but may involve 5-HT_1R, 5-HT_4R, 5-HT_6R or 5-HT_7R [62,82] similar to that observed at CA3 pyramidal neurons, cerebellar synapses and the amygdala [136,196,234].

The ability of postsynaptic 5-HT_{1A}R stimulation to interfere with memory retrieval may involve the inhibition of AC activity and consequent impairment of the activity of PKA. Additionally 5-HT_{1A}R stimulation can inhibit CaMKII activity [221] and the corresponding phosphorylation and increased functionality of AMPAR [42,283] which is necessary for LTP [12].

A role is suggested for the 5-HT_2R family in establishing LTP in the cortex [56,84,85,302] possibly via the alteration of the phosphorylation state of AMPAR. Thus, 5-$HT_{2A/2C}$R ligands may regulate the plasticity of memory retrieval, as ligand-receptor binding would result in increased calcium release from intracellular stores and activation of signaling cascades, resulting in the phosphorylation and synaptic insertion of AMPARs into the PSD [297]. Alternatively, 5-$HT_{2A/2C}$R-induced impairment of memory retrieval may be achieved by inhibiting activation of a PKC-dependent tyrosine kinase signal cascade and a concomitant phosphoryaltion and upregulation of NMDAR as has been recently demonstrated in the basolateral amygdala (BLA) [56,194].

While data on the role of 5-HT in regulating key signaling cascades in many neuronal processes has been documented (*e.g.*, ERK, p38MAPK, PKA/PKC; [31,135,187,315]), the manner in which these signaling cascades that involve these molecular events contribute to the influence of 5-HT systems over processes underlying the storage and retrieval of cocaine-associated memory formation requires further investigation and is an area ripe for exploration.

Serotonergic Manipulations of Cocaine-Associated Memories

The knowledge of neural mechanisms underlying addiction-associated memories is advancing rapidly and the serotonergic signaling pathway signifies a target for exploration of memory processes involved in learning that occurs in the self-administration paradigm. Importantly, the self-administration paradigm must be dissected and explored in the context of other relevant memory tasks. A more detailed understanding of the role of 5-HT_XR manipulations at each stage as well as the molecular and cellular changes involved in memory formation during the various stages of formation of cocaine-associated memories is discussed here (see Fig. 2).

The self-administration assay provides an interesting, but complex, behavioral paradigm for the study of cocaine-associated memories. Chronic cocaine self-administration involves multiple exposures to the drug, the drug-taking context (*e.g.*, self-administration chamber) and all of the discrete stimuli (*e.g.*, stimulus lights, tone) associated with the drug-taking experience for periods of days to weeks. The strength of the associations made between cocaine and the contextual and discrete cues in the self-administration assay are dependent upon several phases of memory processing. To date, there has been limited focus on the processes underlying the specific memory phases of cocaine self-administration learning (*i.e.*, acquisition, extinction, memory retrieval).

The first stage of acquisition (learning) involves the initial linkage of the new experience of cocaine with the contextual and discrete environmental cues. A short-term memory (STM) of this newly acquired experience is formed. This transient and labile memory trace becomes stabilized through a process of **consolidation**, dependent upon new protein synthesis through which STM traces are transformed into stable long-term memories (LTM) [70,81,81,114, 149,202,225,271,281]. This process is associated with long-lasting modifications of synaptic plasticity that are mediated by structural remodeling of existing synapses and addition of new synaptic contacts [46,128]. The self-administration paradigm is perfectly amenable to pharmacological manipulation at the time of learning (during acquisition and consolidation) with the assessment of the effects of such manipulations on cocaine-associated memories accessed during retrieval sessions.

The consolidation of the CS–US associations that are in the process of being formed, for example, might be modified by a specific serotonergic intervention during each cocaine self-administration session when consolidation of STM to LTM is believed to occur. Candidate regions within the brain that may be involved include the BLA, the dorsal hippocampus and subdivisions of the subiculum as recent studies indicate these brain areas as important nuclei involved in the acquisition and consolidation of cocaine-associated memories that maintain cocaine-seeking behavior [17,95,105,106,198,329]. Additional research indicates that new protein synthesis is necessary for the learning and consolidation of cocaine self-administration [216]. An essential role for the cAMP-PKA-CREB pathway has been established for the consolidation process [3,149,254,310]. The knowledge that 5-HT can regulate this pathway (seeSerotonergic Mechanisms in Memory Formation; [8,317]) encourages the design of specific experiments to decipher the role of the serotonergic system in the consolidation and LTM formation of cocaine-associated memories. A possible confound in these experiments is the potential alteration in the reinforcing effects of cocaine induced by the 5-HT_XR manipulation. A potential means to dissociate the effects of serotonergic ligands on the reinforcing effects of cocaine *versus* alterations in learning would be to assess the effects of these ligands during the acquisition versus maintenance stages of self-administration. In most cases, the ability of serotonergic ligands to alter the reinforcing effects of cocaine are measured during the maintenance phase, when levels of responding are stable. During the acquisition phase when the animals are learning the association between operant responding, cocaine delivery and CS presentation, both pre- and post-trial administration of the ligands could be used to temporally dissociate encoding (or acquisition) of information *versus* the consolidation of this information [30,207–209].

An experimental strategy to establish the serotonergic circuitry underlying phases of memory for cocaine-associated memories would involve intracranial microinjection of selective 5-HT_{1B}R, 5-HT_{2A}R or 5-HT_{2C}R ligands into candidate brain nuclei. Pretraining administration of specific 5-HT_XR ligands into the discrete brain region would allow analysis of involvement in the acquisition of the CS-US pairing upon testing in a subsequent retrieval session. Post-training manipulation of 5-HT_XR at variable intervals (1 – 6 hours) after each training session would specifically answer the query as to whether a specific 5-HT_XR manipulation can disrupt the consolidation of the CS-US memory in the cocaine self-administration paradigm.

A typical experimental paradigm involves completion of the acquisition phase to achieve stable performance in a cocaine self-administration followed by extinction training. As yet another (now novel) learning process, extinction training may reverse neuroadaptations normally observed during cocaine withdrawal and/or evoke new adaptations due to the novel extinction learning [79,285,290,304]. For example, while levels of tyrosine hydroxylase (TH), the rate-limiting enzyme for DA synthesis, were decreased in the nucleus accumbens (an area implicated in conditioned reward [156,277]) during withdrawal from cocaine self-administration, extinction training reversed this deficit, restoring/normalizing TH levels to those observed in untreated controls [285]. These results demonstrate that extinction-experienced animals differ from a neurobiological standpoint when compared with animals in cocaine withdrawal alone and also suggests that strategies that incorporate extinction training offer treatment strategies that could produce substantial long-term benefits.

Extinction sessions (or exposure-based therapies) are successfully employed to weaken pathogenic memories that are responsible for various anxiety disorders [72,100], however, extinction procedures have had limited therapeutic success in reducing relapse among drug-dependent patients [57,64,73,102,130,151,239]. There is a pervasive thought that if optimal parameters for cue exposure could be discovered (*e.g.*, the right cues chosen, the appropriate number of sessions conducted), treatment strategies that incorporate extinction training behavior in conjunction with pharmacological treatment might increase treatment efficacy

[64]. Similar to CS-US training that occurs during acquisition, extinction training incorporates acquisition and consolidation processes. Administration of 5-HT_XR ligands that facilitate learning and memory before each extinction session may enhance extinction learning while 5-HT_XR ligand administration after each extinction session might enhance consolidation, leading to improved effectiveness and/or shortening of the duration of extinction learning [71].

Consolidated memories appear to become labile again after "**reactivation,**" that is, soon after the memory is retrieved by reminder stimuli that apparently reactivate the original memory trace [219], as is the case in the cue-reinstatement model. In the case of cocaine self-administration [182], re-exposure to the CS ("reactivation") might trigger the retrieval of CS–US associations and induce two competing processes known as "reconsolidation" and "extinction," which are dependent on the duration and offset of the CS re-exposure event [76,81,247,249]. The so-called **reconsolidation** upon brief exposure to the conditioned stimuli requires *de novo* protein synthesis for the maintenance of the memory [226,227]. Reconsolidation is believed to ensure that the fragile memory returns to a stable state [225, 279] and may provide a window in which to manipulate long-lasting drug-associated memories.

While much debate exists as to the similarities and/or differences between the original consolidation process and the reconsolidation phase, the predominant thinking is that the two processes engage distinct brain areas and molecular pathways [3,4,183]. The involvement of specific intracellular pathways in the molecular mechanisms underlying reconsolidation of cocaine-associated memories have been partially described and include activation of PKA, ERK, CREB and zif268 [27,161,168,184,217] and release of 5-HT [45]. The recent study by Canal and colleagues [45] reported that intra-amygdala injections of the protein synthesis inhibitor anisomycin resulted in the release of 5-HT near the site of injection. The authors suggest that 5-HT (along with other neurotransmitters) may be involved in the mechanisms through which anisomycin inhibits *de novo* protein synthesis and disrupts reconsolidation of a previously formed memory [45,115,273].

During the reconsolidation process, memory traces become labile and can be altered by various pharmacological manipulations [321]. To date, evidence from various studies suggests that administration of non-specific protein synthesis inhibitors (*e.g.*, anisomycin), if applied immediately after memory retrieval, blocks subsequent expression of a previously acquired conditioned response [81,225]. As protein synthesis inhibitors do not easily cross the blood-brain barrier and can be toxic, they are unlikely to be used in studies in humans. Thus, future experiments with more benign compounds, such as selective 5-HT_XR ligands, administered to animals acutely following a CS-retrieval session to reduce later memory expression (possibly through inhibiting reconsolidation mechanisms) are necessary to further delineate the role of serotonergic systems in reconsolidation of cocaine-associated memories. If 5-HT release is an early trigger in the cascade of events that control new protein synthesis required for memory reconsolidation processes [45], then inhibition of 5-HT release following the re-activation session might be expected to increase protein synthesis and facilitate the reconsolidation of the predominant memory that was retrieved during the session (see below). If the session is of long duration then facilitation and stabilization of the extinction memory would be expected.

Prolonged re-exposure to the CS in the absence of the US triggers the formation of a new memory trace that encodes the dissociation between the CS and the US (CS–no US; extinction memory), therefore competing with the original memory (CS–US) [305]. Thus, a drug that enhances the retrieval of the extinction memory (*i.e.*, the consolidation of the CS–no US association) may also reduce the impact of cocaine-associated memories. Research indicates that the competing processes of reconsolidation and extinction require different molecular components [314] and inhibition of protein synthesis at this stage blocks the formation of this

new extinction memory, leaving expression of the original memory unchanged [305]. To date, most studies which examined the effects of serotonergic ligands on retrieval of cocaine-associated stimuli employed an extinction phase within the self-administration protocol. Specific experiments have not yet addressed the question as to whether the 5-HT_XR ligand altered retrieval of the original memory (CS-US) or the novel extinction memory (CS-no US). Studies to determine whether the impairment in cocaine-associated memories in subsequent reactivation tests involves disruption of reconsolidation or a potentiation of extinction would require regulating the re-exposure sessions and perhaps a comparison to a "forced abstinence" period. Re-exposure sessions of short duration (15 min) would ensure reconsolidation processes whereas longer sessions (1–3 hrs) would involve consolidation of CS-no US memories [261].

Knowledge of the mechanisms through which 5-HT_XR manipulations may disrupt cocaine-associated memories after a period of forced abstinence *versus* extinction is also critical for understanding of cocaine-associated memories. Humans rarely undergo extinction *per se*, but rather, cease using drugs for other reasons, [88] and as noted, extinction procedures to date have been of limited therapeutic success in reducing relapse among drug-dependent patients [57,64,73,102,130,151,239]. It has also been suggested that animal models of cocaine-seeking assessed after forced abstinence may have stronger face validity for cue-induced relapse in humans relative to cocaine-seeking measured after explicit extinction training [104]. A relatively unexplored area is the effect of repeated ligand administration on the impact of cocaine-associated cues in the retrieval test. This is an important area of research as a medication with efficacy as an abstinence enhancer would be administered to cocaine-dependent patients beginning at termination of cocaine use and continuing for a period of time. For example, in a 12-week, double-blind placebo-controlled trial [220], the SSRI citalopram (Celexa®) in conjunction with contingency management significantly increased treatment retention and reduced craving and cocaine-positive urines in outpatient studies of cocaine-using subjects.

Understanding the role of 5-HT in the neural systems underlying consolidation, reconsolidation, reactivation and extinction and their special properties *vis à vis* drug-associated cues will open the door to selectively minimizing the strong stimulus properties of cocaine-associated memories [92,182,184]. Armed with this knowledge, we can then hope to develop serotonergic pharmacotherapies to specifically target processes underlying cocaine-associated memories.

Conclusion

One of the most challenging endeavors in neuroscience is to identify the molecular mechanisms that underlie drug-associated memory formation. While the role of specific serotonergic receptors in learning and memory processes underlying cue-evoked drug-seeking behavior is still under-examined, this is an area ripe for further investigation. The acquisition of cocaine-associated memories involves storage and encoding of cue-reward associations, and the expression of cue-induced drug-seeking behavior involves the retrieval of memories of such cue-reward associations (Fig. 2). While to date the attenuation of the incentive motivational effects of cocaine-associated cues has been proposed as the mechanism by which serotonergic regulation modulates drug-seeking behavior [36,38,98,99,231,233], serotonergic ligands may inhibit cue-induced drug-seeking behavior by interfering with aspects of memory encoding and retrieval [104,184,298], either by blocking retrieval of the original CS-US memory or facilitating the retrieval of the CS-no US association. These processes may involve modifications of the functional status of the targets within the serotonergic system (*e.g.*, transporter, 5-HT_XR or linked downstream signaling partners [43,149,209]) which contribute to the ability of serotonergic ligands to disrupt retention of a conditioned association between

cocaine and environmental stimuli. Further research efforts to explore the manner in which 5-HT manipulations, in particular those involving 5-HT_{1B}R, 5-HT_{2A}R and 5-HT_{2C}R, regulate consolidation, retrieval or reconsolidation of memory at molecular, cellular and behavioral levels, may clarify these potential mechanisms in reducing cue-elicited drug-seeking behavior and open new avenues to therapeutically enhance abstinence.

Abbreviations

5-HT, 5-hydroxytryptamine (serotonin)
5-HT_XR, 5-HT receptor family
8-OH-DPAT, 8-hydroxy-2-(di-*n*-propylamino)tetralin
AC, adenylate cyclase
AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptors
BLA, basolateral amygdala
cAMP, c**yc**lic adenosine monophosphate
CaMKII, calcium/calmodulin-dependent kinase type II
CR, conditioned response
CREB, cAMP response element binding protein
CS, conditioned stimulus
D_XR, dopamine receptor
DA, dopamine
DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane
ERK, extracellular signal-regulated kinase
FR, fixed ratio
GPCR, G-protein coupled receptor
IP, inositol triphosphate
LTD, long-term depression
LTP, long-term potentiation
NMDA, *N*-methyl-D-aspartate receptors
p38 MAPK, p38 mitogen-activated protein kinase
PKA, cAMP-dependent protein kinase
PKC, protein kinase C
PLC, phospholipase C
PSD, post-synaptic density
Ras-GTPase, Ras-guanosine triphosphatase activating protein
SSRI, selective serotonin reuptake inhibitor
SERT, 5-HT transporter
TH, tyrosine hydroxylase
TPH, tryptophan hydroxylase
US, unconditioned stimulus
US, unconditioned stimulus
VTA, ventral tegmental area

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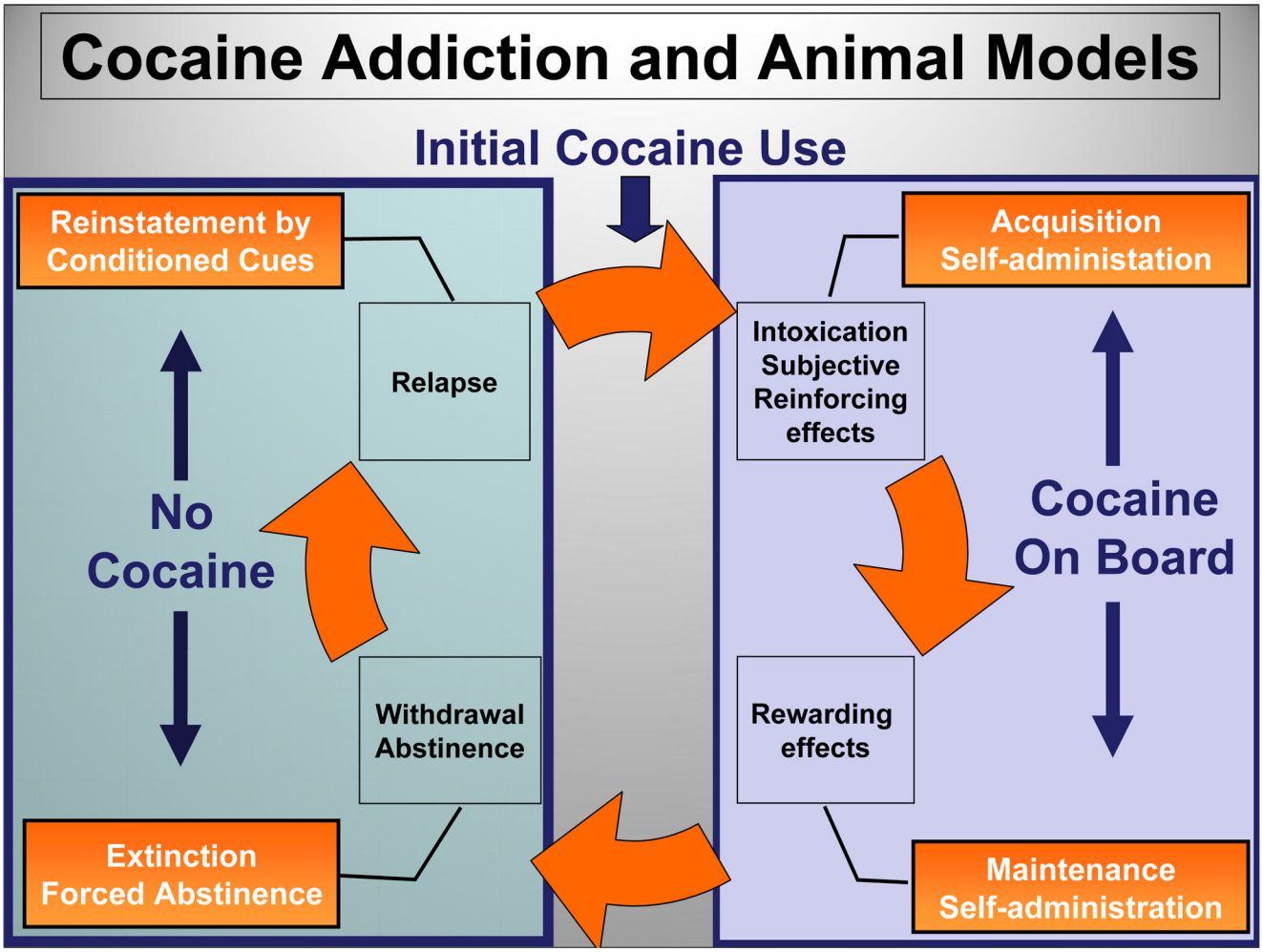

Fig. 1. Cocaine Addiction and Animal Models

Addiction to cocaine or other abused substances is a chronic relapsing disorder characterized by persistent and compulsive drug-seeking and -craving that endures even after years of abstinence (adapted from [170,171]). The right side of the figure illustrates the component of the addictive cycle which is associated with the use of cocaine ("Cocaine on Board"). With initial use of cocaine, the ***intoxication*** (euphoria) and other ***subjective effects*** reinforce the behavioral output needed to continue drug use ***(reinforcing effects);*** these ***reinforcing effects*** increase the probability that drug-taking behavior will reoccur. The animal model of self-administration is useful to analyze the acquisition and consolidation of the learning of drug-taking behavior. A pleasurable subjective experience forms the basis of the ***rewarding effects*** of the drug, which play an essential role in its ability to serve as a reinforcer. The maintenance phase of self-administration is described by stable performance of the operant for delivery of cocaine and provides a window to investigate manipulations that alter expression of the behavior. The left side of the figure illustrates the component of the addictive cycle which is associated with the cessation of cocaine use ("No Cocaine"). The decision to cease using cocaine may be made voluntarily by the addict or under circumstances of duress, for example, under court-mandated treatment. Upon ***withdrawal*** from long-term use of this psychostimulant, abusers exhibit psychiatric symptoms characterized by both psychological (e.g., depression, anxiety, anhedonia, craving) and physiological symptoms (e.g., fatigue, hyperphagia, anergia). Once the ramifications of detoxification and withdrawal are handled,

the addict enters a period of ***abstinence*** from cocaine use which may last from days to years. In self-administration models, behavioral components and neural mechanisms underlying abstinence may be investigated after a period of extinction or forced abstinence. However, abstinence is challenged by the potential for relapse to renewed use of cocaine. The reinstatement model of self-administration is useful for analysis of this phase of the addictive cycle as modeled by an animal homologue. Three major factors that may initiate drug-seeking behavior and relapse to drug use include exposure to drug-associated environmental stimuli, a “priming” or non-contingent dose of the drug itself or stress.

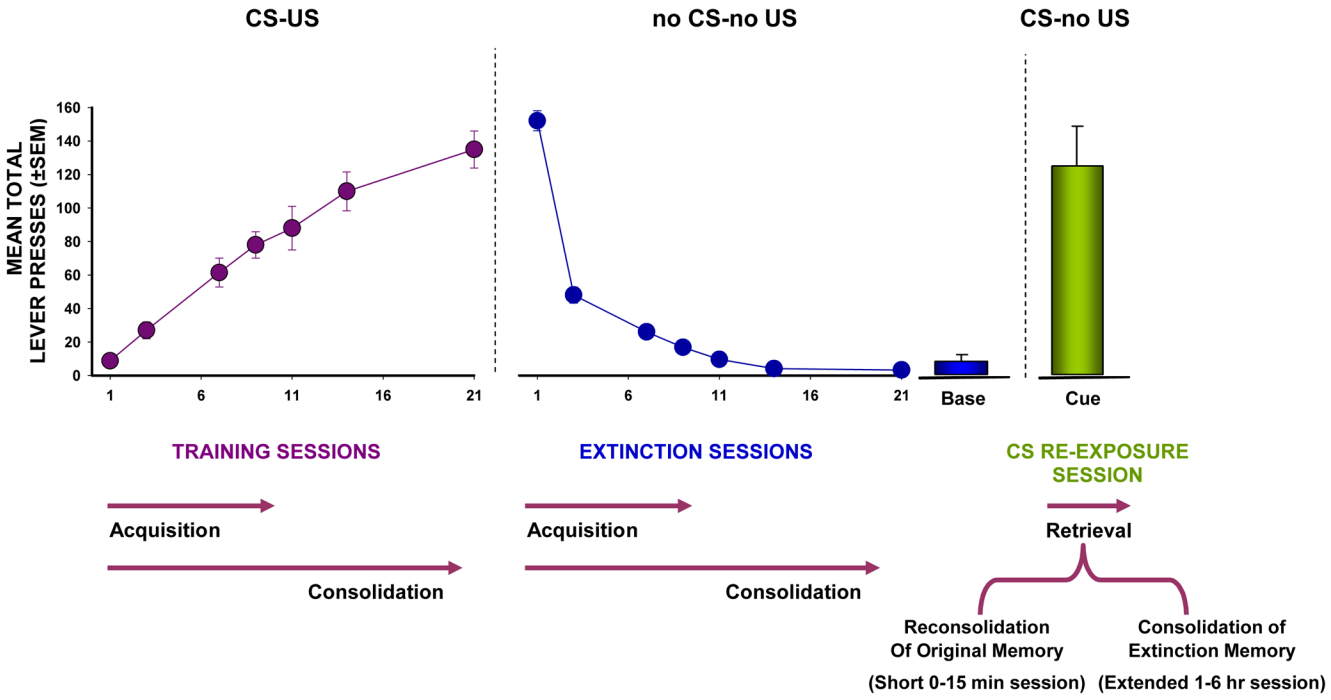

Fig. 2. Memory Processes Underlying Cocaine-Associated Memories in the Self-Administration Paradigm

A typical cocaine self-administration paradigm involves completion of acquisition, extinction, and reinstatement phases. For illustrative purposes, the data are represented as mean (±SEM) lever presses per session during each stage of cocaine self-administration. The learned linkage between the cocaine-taking contextual (diffuse) cues, the salient (discrete) environmental cues [conditioned stimulus (CS) complex] previously paired with cocaine delivery (*e.g.*, tone, stimulus, light), and the effects of cocaine (US) occurs during the acquisition phase (CS-US association). In most studies of reinstatement of drug-seeking, extinction of the behavior is established in the absence of the drug (no US) and the CS complex (no CS) resulting in the weakening of the association between the behavior (lever press, nose poke) and delivery of the primary reinforcer (cocaine). The previously established CS-US association is not eliminated but rather suppressed by new learning during extinction (no CS-no US association). Both acquisition of original (CS-US) and extinction (no CS-no US) learning are subject to consolidation processes requiring protein syntheses in which the STM of these associations are converted into LTM. Once lever press responding has achieved a low, stable baseline level ("Base"), the effectiveness of cue-induced reinstatement can be assessed ("CS"). The magnitude of operant responses on the previously drug-paired operandum upon re-exposure to the CS complex in the absence of actual cocaine delivery can then be quantified as a measure of drug-seeking behavior supported by the CS complex. The cue re-exposure session upon re-introduction of the CS complex may lead to retrieval and subsequent reconsolidation of the original self-administration memory (CS-US) or retrieval and consolidation of the newly formed extinction memory (no CS-no US) depending on the session duration.