Neuroanatomical Structures Underlying the Extinction of Drug-Seeking Behavior

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Abstract: This review summarizes current knowledge about the neurobiological components underlying the extinction of drug-associated memories and how they may contribute to the treatment of drug addiction. Evidence suggests that extinction learning is not the forgetting, or unlearning, of the associations between external stimuli and drug effects, but that new reinforcer expectancies are necessary for extinction of drug-seeking behavior to take place. Several theories suggest that addiction is a disorder of learning and memory, and recent evidence indicates that the brain circuits, neurotransmitters, and signal transduction mechanisms that underlie drug addiction are similar to those that mediate learning and memory processes. According to these theories, drug addiction results from repeated drug use and the formation of lasting associations between a drug's effects, withdrawal symptoms, and the environmental cues and contexts within which they are experienced. Unfortunately, standard behavioral modification techniques, such as cue exposure therapy, have shown only moderate efficacy in reducing and/or extinguishing the salience of drug-associated cues and contexts. Therefore, a greater understanding of the neurobiological mechanisms involved in the extinction of drug-related memories could provide novel therapeutic interventions for the treatment of drug addiction.

Keywords: Addiction, extinction, learning, neurobiology, drug memories, treatment, drug context.

INTRODUCTION

Drug addiction is a disorder of the nervous system marked by a transition from intermittent drug use to compulsive, uncontrolled drug intake and repeated attempts at abstinence and relapse. It is now apparent that the brain circuits, neurotransmitters, and signal transduction mechanisms that underlie drug addiction have considerable overlap with those mediating normal learning and memory processes [1-4]. Therefore, drug addiction has been theorized to be a disorder of learning and memory [1-11]. Many of these theories suggest that drug addiction results from instrumental and associative *overlearning* whereby drugs and environmental cues and contexts become *hypersalient* leading to drug craving and relapse [12-14]. As a result, long-term drug use leads to the formation of compulsive, habitual, and ritualistic drug-taking behaviors

Attempts to extinguish the salience of drug conditioning by behavioral modification techniques such as *cue exposure therapy* have only shown limited success [12, 15-19]. Additionally, most current behavioral and pharmacological treatments for addiction center on eliminating withdrawal symptoms or reducing drug intake with little focus on the process of extinction. A greater understanding of the neurobiological mechanisms involved in the extinction of drug-related memories and drug-seeking behaviors could provide novel therapeutic interventions for the treatment of drug addiction.

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The majority of studies examining the neural mechanisms of extinction have focused on either appetitive conditioning (e.g., extinction of consummatory behavior related to natural rewards such as food or sucrose) or aversive conditioning (e.g., extinction of fear-related behaviors following pairing of environmental stimuli with electric footshock). However, relatively few studies have attempted to identify the neural mechanisms that underlie the extinction of addiction-related behaviors such as compulsive drug-seeking and conditioned associations between drugs of abuse and environmental stimuli.

WHAT IS EXTINCTION?

Extinction is defined as the gradual elimination of a learned response that occurs when the response is no longer reinforced or the unconditional stimulus (US) is no longer presented in conjunction with the conditioned stimulus (CS). Thus, after the repeated pairing of a discrete CS (e.g., light) with US (e.g., shock) the CS will elicit specific behaviors because the CS now predicts the availability of the US. With repeated presentations of the light without the shock, the conditioned response dissipates, or is extinguished, since the light no longer "predicts" that the shock is imminent. Within the context of drug addiction, a drug (US) is often administered in a particular context (CS). In the same manner that a light can be conditioned to elicit behaviors related to the presence of a shock, cues conditioned to drug availability can elicit behaviors that induce drug use (e.g., craving). The process of extinction differs from that of *reconsolidation*, which is the process of restabilizing a memory after it has been *reactivated* through stimulus re-exposure [20, 21]. While yet to be shown experimentally, it is believed that reconsolidation would enhance a specific association between a drug and environmental stimulus.

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Alternatively, disruption of this process causes amnesia [22, 23]. This knowledge has led to a resurgence of interest in the extinction process as a potential treatment strategy for drug addiction. Extinction, in theory, would serve to create new associations that would replace the initial learning of the association between a drug's subjective effects, environmental cues, and persistent maladaptive memories [24].

EVIDENCE THAT EXTINCTION IS NEW LEARNING

For many years following landmark studies by Ivan Pavlov and B.F. Skinner in the fields of associative and operant learning and memory, it was assumed that the extinction of classically- and operantly-conditioned behaviors was a process of "forgetting" or "unlearning" of the relationships between external stimuli and behavioral responses. However, over the last two decades there has been a tremendous amount of evidence that the extinction process is a form of new and active learning that challenges the previously held belief that extinction is simply forgetting or weakening of learned associations. This is evidenced by the fact that:

1. Drug-seeking behavior can be reinstated by several stimuli including a priming injection of the drug, presentation of drug-associated environmental stimuli, or exposure to an acute stressor without the need for additional behavioral training in a phenomenon known as *reinstatement* [25-40]. The fact that no added behavioral training is necessary suggests that a memory trace of the original association remains intact. Therefore, extinction is likely to incorporate the formation of new stimulus-reward associations.

2. Drug-seeking behavior can spontaneously resume following extensive extinction training [15, 41-44] in a process known as *spontaneous recovery*. This behavior suggests that the neural processes underlying drug self-administration remain intact.

3. Extinction of conditioned behaviors is context specific [45-51]. Take, for example, the *renewal* effect or *contextual reinstatement*. This is the phenomenon by which animals are trained to self-administer a drug in one environment and then that behavior is extinguished in a different environment. If the animal is placed back into the environment where the contingencies were originally established, drug-seeking behavior will resume [52].

4. The re-training of animals to self-administer a drug following extinction takes significantly less time compared to the initial training process [53, 54]. This process is known as *reacquisition* and suggests that the original learning during training of the self-administration procedure generally remains unaltered.

5. Studies utilizing fear conditioning show that extinction training induces cellular neuroadaptations that underlie normal learning and memory, such as long-term potentiation (LTP) and *de novo* protein synthesis [55, 56]. This evidence reveals that the neural mechanisms mediating learning and memory may also contribute to extinction training and that extinction is indeed a process of new and active learning.

These lines of evidence suggest that extinction learning is not the "forgetting" of previously learned contingencies between environmental stimuli and drug availability. Instead, it appears that the original associative and instrumental learning that takes place during the initial stages of addiction remain intact, and for extinction of drug-seeking behavior to take place, there must be a formation of new reinforcer expectancies [47].

RODENT MODELS OF DRUG ADDICTION AND EXTINCTION LEARNING

Several animal models, primarily using rodents, have been developed to study the various aspects of drug addiction [25, 26]. Those procedures that are most appropriate for the study of extinction learning include the *intravenous drug self administration* (IVSA), *conditioned place preference* (CPP), and *cue- and context-induced reinstatement of drug-seeking behavior* paradigms.

Conditioned Place Preference (CPP)

In the CPP paradigm, the animal learns to associate the subjective and physiological effects of a passively administered drug with the environmental context in which it is received. A typical CPP apparatus consists of two separate compartments. Each compartment has unique tactile and visual characteristics and together, they are connected by a neutral "start" box. Both compartments are typically equipped with photobeams that detect the presence and measure the locomotor activity of the animal. During the initial phase of the experiment, the animal is allowed access to both compartments for a set amount of time in order to determine preference (measured by total time spent in each compartment) between the two environments. Next, the animal is injected with a neutral substance (e.g., saline) and is confined to the initial preferred environment. On the following day, the animal is injected with the conditioning drug and confined to the initial non-preferred environment. This process is repeated for a set number of days (typically 4-6 times) and each animal receives equal pairings of the saline/context and drug/context. During the conditioning trials, the animal learns to associate the subjective effects of the drug with the unique physical characteristics of that compartment. In the final phase of the experiment, the animal is again allowed free access (in a drug-free state) to both compartments to determine the post-conditioning preference for each environment. If the animal now shows a significant increase in time spent in the drug-paired environment (the one that was initially non-preferred) then a CPP has been established and provides indirect evidence of the reinforcing effects of the drug. Multiple variations of the CPP procedure have been implemented (e.g., nonbiased design that results in no initial preference to either environment) and conditioned preferences have been established for nearly all drugs of abuse [57].

Similar to the IVSA paradigm, the CPP paradigm can be used to assess extinction learning. To accomplish this, the drug-paired side can be either repeatedly paired with saline or the established CPP can be allowed to dissipate over a period of time by repeatedly testing the animal's preference without further conditioning trials. Extinction of a CPP is typically measured in number of days required to reach extinction criteria and, as in the IVSA paradigm, a treatment

that reduces the number of sessions required to reach this criteria is thought to reflect either enhanced extinction learning or disruption of drug/context memory availability.

Intravenous Drug Self-Administration (IVSA)

In the rodent IVSA paradigm, animals are trained to perform some type of operant task (usually a bar press or nose poke) in order to receive an intravenous infusion of, or access to, a drug. During the acquisition phase, animals are trained to perform the operant task with a non-drug reinforcer, such as food. Each reinforcer delivery is accompanied by the presentation of a visual and/or auditory stimulus (e.g. light or tone) that allows for the acquisition of a reinforcer/cue stimulus association. After the task has been successfully acquired, the non-drug reinforcer is replaced with an abused drug (such as cocaine, heroin, methamphetamine, nicotine, alcohol, etc.). During the maintenance phase, self-administration sessions are continued for a pre-defined number of sessions until responding for the drug becomes stable.

In the extinction phase, each previously drug-reinforced response results in either no programmed consequence or saline infusion. As extinction training continues, there is a gradual decrease in the number of responses that previously resulted in drug delivery; which is interpreted as the animal learning that the operant response no longer produces drug availability. An experimental treatment that decreases the number of tests required for predetermined extinction criteria is interpreted as either an enhancement of extinction learning or a disruption of drug/contextual stimulus memory availability. The previously reinforced operant response displayed during extinction training is referred to as *drug-seeking behavior* because the response is not drug-reinforced.

Cue- and Context-Induced Reinstatement of Drug-Seeking Behavior

The reinstatement model is a widely used animal model of relapse [25-27, 29, 32, 58, 59] in which animals are trained to perform an operant task in order to receive an infusion of a drug. *Cue-induced reinstatement* examines the strength of the reinforcer/cue stimulus association acquired during self-administration. Following the initial training and extinction training described in the IVSA paradigm above, the animal is returned to the experimental apparatus and, in a response-contingent or non-contingent manner, presented with the cue previously associated with each drug infusion. Here, the animal's extinguished operant response is *reinstated*, although it does not actually result in the delivery of an infusion of the drug. This provides a tool for measuring the motivational salience of the cue, independent of the psychomotor effects of the drug. In a slightly different paradigm, *context-induced* or *contextual reinstatement* examines the associative strength of the physical environment in mediating drug-seeking behavior [52, 58, 60-64]. Here, animals undergo extinction training in an experimental apparatus that is contextually unique from the apparatus where self-administration was acquired. This contextual change can involve modification of the floor, odor, and colors on the wall. Upon completion of extinction, the animal is returned to the original apparatus in which drug self-administration occurred. This reinstatement of context evokes an increased number of operant responses that previously resulted in the delivery of a drug as a result of the associative strength between the physical environment and drug.

The Neurobiological Substrates of Extinction Learning

There is a significant overlap between the neuroanatomical circuits and neurochemical substrates that underlie learning and memory processes and those that mediate drug addiction. For instance, both learning and memory and drugs of abuse induce LTP and long-term depression (LTD) [4, 6, 65-68]. Unfortunately, most of what is known about the neural mechanisms of extinction learning was derived from studies that use aversive conditioning (e.g., footshock) or appetitive conditioning with natural rewards (e.g., food). The extinction of conditioned fear in both animals and humans [69-80] as well as a cocaine CPP [81-83] can be facilitated by the cognitive enhancing drug D-4-amino-3-isoxazolidone [D-cycloserine (DCS)], which is a partial agonist at the strychnine-insensitive glycine site of N-methyl-D-aspartate (NMDA) receptors [84, 85]. Nic Dhonnchadha and colleagues recently found that DCS enhances the extinction learning process and inhibits reacquisition of drug self-administration in rats trained to self-administer cocaine [86]. However, while the neural mechanisms involved in the extinction of a drug memory may be similar, it would be naïve to assume that they are identical to those involved in conditioning to non-drug reinforcers. Therefore, this review summarizes what is currently known about the neurobiological components underlying the extinction of drug-associated memories and how they may contribute to the treatment of drug addiction.

THE PREFRONTAL CORTEX

Functional Role and Anatomical Connectivity

The prefrontal cortex (PFC) is a collection of regions in the dorsal forebrain made up of the medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), and anterior cingulate cortex [87]. The mPFC is comprised of multiple subregions including the dorsomedial PFC (dmPFC), [comprised mainly of the prelimbic cortex (PrLC)], and ventromedial PFC (vmPFC), [mainly made up of the infralimbic cortex (ILC)] while the OFC is divided into medial (mOFC) and lateral (lOFC) sections. The PFC is considered the executive center of the brain due to its involvement in a multiplicity of functions. These include goal-directed behaviors, impulsivity and response inhibition, reward expectancy, salience attribution, emotional learning, drive and motivation, decision making, selective attention [88-91], memory consolidation, which can be defined as the process of stabilizing, storing, and strengthening new memories [92], as well as memory recall, which can be defined as the reactivation and/or retrieval of a previously consolidated memory [93].

The PFC is connected to a number of other brain regions including the brainstem, thalamus (which acts as an intermediary between the PFC and dorsal and ventral striatum), limbic system (including the amygdala and hippocampus), as well as other cortical regions [94-97]. The PFC interacts with other regions of the brain through a broad and diverse network of neurotransmitter systems [96]

including afferent dopaminergic projections from the ventral tegmental area (VTA) [98], glutamatergic projections from thalamus, hippocampus, and amygdala [91]; efferent transmission to VTA and nucleus accumbens (Acb) [96, 99], gamma-Aminobutyric acid (GABA) interneurons [100, 101]; serotonergic innervation from the median and dorsal raphe nuclei [102-104], noradranergic innervations from the locus coeruleus [105-107], and cholinergic innervation from nucleus basalis magnocellularis, diagonal band, and mesopontine laterodorsal nucleus [108-111]. Moreover, there are also various peptidergic systems present within the PFC including opioid peptides, cholecystokinin (CCK), neurotensin, neuropeptide Y (NPY), and corticotropin releasing factor (CRF) [112].

Role in Extinction Learning

There is extensive research implicating the PFC in the extinction of conditioned fear (see [113-115] for comprehensive reviews). Fear conditioning is a form of classical conditioning in which a particular neutral context (e.g., operant chamber) or neutral stimulus (e.g., light or tone) is paired with an aversive stimulus such as an electric footshock. After repeated pairings, presentation of the neutral stimulus elicits fear, which can be measured with galvanic skin response and/or freezing behavior (e.g., crouching time).

Evidence suggests that the PFC plays a critical role in the consolidation of extinction learning [116]. Lesions or temporary inactivation of the ILC and vmPFC inhibit extinction of conditioned fear [113, 115, 117-125], block retrieval of extinction learning [116], and result in behavioral perseveration in both rodents [120] and primates [88]. Inhibition of protein synthesis or mitogen-activated protein kinase (MAPK) activity [126-128], antagonism of NMDA receptors [129-130], as well as pharmacological inactivation of the ILC impairs extinction memory and the retrieval of a consolidated memory [122]. The vmPFC role in the consolidation of extinction learning might involve regulation of NMDA receptors that mediate molecular cascades necessary for normal learning and memory as recent animal research shows that inactivation of vmPFC NMDA receptors [*via* NMDA antagonist 3-(+-)2-carboxypiperazin-4yl propel-1 phosphate (CPP)] inhibits extinction learning [129]. PFC stimulation enhances extinction of conditioned fear [131-133] and neurons in the PFC have been shown to alter their transmission during extinction training [131]. Furthermore, human imaging studies show a positive correlation between activity levels in the vmPFC and extinction of conditioned behaviors [134, 135].

Much less is known about the PFC's role in extinguishing drug-related memories and drug-seeking behavior, but there appears to be considerable overlap between those mediating extinction of fear and drug conditioning (see [136] for a recent review). Peters and colleagues have shown that enhanced activity in the ILC inhibits drug-seeking and blocks reinstatement [137]. Pharmacological inactivation of the ILC facilitated the reinstatement of drug-seeking behavior whereas activation of the ILC with α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) blocked the reinstatement of cocaine-seeking behavior. Furthermore, unilateral inactivation of the nucleus accumbens shell (AcbSh) had little effect on reinstatement of drug-seeking behavior whereas simultaneous inactivation of the AcbSh and ILC attenuated cocaine-seeking behavior. These results suggest a unique pathway between the ILC and AcbSh that regulates extinction of drug-seeking behavior [137].

Available evidence suggests that long term drug exposure reduces functionality and activity in the PFC [138, 139] and that this reduction of activity and functionality inhibits impulse control and fosters the development and/or enhancement of incentive salience attributed to drug-related cues and memories [138, 140]. It's worth noting that drug addicts exposed to drug-associated stimuli show increased activation within the OFC and ACC [141-149], possibly due to the inhibition of brain regions that are necessary for extinction learning [142]. One study in non-human primates supports the notion that the PFC regulates the transition from automatic to controlled behaviors [150], which could be helpful in understanding why a drug addict would struggle in attempting to self-regulate behaviors that are compulsive and uncontrolled.

The Amygdala

Functional Role and Anatomical Connectivity

The amygdaloid complex is a part of the limbic system located within the temporal lobe ventral to the caudate-putamen (CPu) and globus pallidus (GP) and lateral to the piriform cortex (Pir). The amygdala is made up of four major subdivisions, including the basal subdivision [mainly comprised of the basolateral amygdala (BLA)], the medial subdivision (which includes the basomedial nucleus, intraamygdalar stria terminalis, intercalated nuclei of the amygdala, and medial amygdala), the lateral subdivision (or, lateral amygdala), and the central subdivision (central nucleus of the amygdala). The amygdala is involved with various learning and memory processes including the formation and consolidation of emotional memories [151, 152]. More specifically, the BLA plays a crucial role in the synaptic plasticity associated with emotion-related behaviors and processing of emotionally significant stimuli [10, 134, 152-157] as well as the formation of stimulus-reward associations [33, 158-164].

Within the amygdala there is a broad and diverse network of neurotransmitter systems [165] including glutamatergic, cholinergic, GABAergic, dopaminergic, noradranergic, and serotonergic terminals and receptors. Neuropeptides such as enkephalins, CRF, NPY, and CCK and their receptors are also present in the amygdala. Afferent and efferent sources and targets include all sensory cortices, PFC, medial temporal lobe/hippocampus, hypothalamus, bed nucleus of the stria terminalis, brainstem, and striatum (involved only in efferent activity) [166]. The amygdala receives sensory input from all of the sensory cortices and contextual/episodic information from the hippocampus and these connections may mediate the formation of drug-related memories [167]. Efferent projections, possibly underlying activation of the neurocircuitry mediating reward/reinforcement, are sent from the amygdala to the VTA and Acb. Additional efferent signals are sent from the amygdala to the hippocampus, CPu, and frontal cortex possibly facilitating contextual learning

and memory, motor learning, and activation of the executive control center of the brain, respectively [158].

Role in Extinction Learning

The BLA plays an integral role in the formation of associations between drugs of abuse and environmental cues and contexts [168-172] as well as the relationship between negative affective states due to withdrawal and the environmental cues and contexts experienced in those aversive states [173]. Conditioned fear studies have provided evidence that inhibition of normal learning and memory components within the BLA such as NMDA receptor function [174, 175], MAPK [176], phosphatidylinositol 3-kinase (PI-3K) [177], L-type calcium channels [178], calcineurin [177], and *de novo* protein synthesis [176, 178, 179] attenuate the extinction of conditioned fear. Therefore, activity in the BLA appears to be necessary for drug-related cues and contexts to influence instrumental behavior [180, 181] such as cue-induced reinstatement of cocaine-seeking behavior [182, 183]. Furthermore, both current and former drug addicts exposed to drug-related cues (e.g., pictures of needles or drugs) show increased activity in the amygdala [184, 185].

Manipulation of various neurotransmitter systems in the BLA has been shown to affect the extinction of drug-seeking behavior. Facilitation of glutamatergic transmission enhances extinction of drug-seeking behavior [81, 83, 186-188]. It is likely that additional neurotransmitter systems, including dopamine and acetylcholine, are also involved in the extinction of drug-cue/context associations [3, 189-191]. Several recent studies have shown that enhancement of cholinergic and glutamatergic transmission in the BLA facilitates the extinction of a drug-paired CPP [81, 190]. Schroeder and Packard have shown that the extinction of an amphetamine CPP involves cholinergic transmission in the BLA. In this study, direct infusions of the muscarinic acetylcholine receptor agonist oxotremorine facilitated the extinction of an amphetamine CPP [190]. In a previous study, these same investigators showed that local infusions of glucose also facilitated extinction of an amphetamine CPP [192]. Botreau and colleagues enhanced NMDA receptor function, which has been shown to mediate the consolidation of drug-related memories [184, 185, 193], with local infusions into the BLA of DCS to facilitate the extinction of a cocaine CPP [81]. In this study, control animals maintained a preference for the cocaine-paired chamber until their sixth extinction session whereas DCS treated animals extinguished a cocaine CPP after only three extinction sessions and maintained a neutral preference in extinction tests 3 and 14 days later [81]. Taken together as a whole, these findings suggest that the amygdala is involved in the extinction of drug-cue associations [81, 189, 190, 192].

THE HIPPOCAMPUS

Functional Role and Anatomical Connectivity

The hippocampus is a densely packed scrolled structure located within the medial temporal lobe that can be divided into several subregions including the dorsal hippocampus [which includes the dentate gyrus (DG) and cornu ammonis 1 (CA1)], ventrolateral hippocampus (which includes the subiculum and cornu ammonis 3 (CA3) and 2 additional cornu ammonis regions (CA2 and CA4) [194]. There is a continuous pathway of information moving through the hippocampus that originates and terminates at the sensory cortices and also that begins in the hippocampus at a gap between the subiculum and DG known as the perforant pathway [151, 194, 195]. After information enters the hippocampus, the entorhinal cortex (EC) synapses on cells in the DG which projects to CA3, then onto CA1, and back to the subiculum. The subiculum then regulates the transmission of information to the hypothalamus and mammillary bodies (*via* the fornix) or the relay of information to the EC thereby propelling information back to the sensory cortex [194, 196]. Afferent projections are received from a number of subcortical inputs including the amygdala, medial septum and diagonal band of Broca, claustrum, substantia innonminata and basal nucleus of Meynert, thalamus, lateral preoptic and lateral hypothalamic areas, supramammillary and retromammillary regions, VTA, tegmental reticular fields, raphe nuclei, dorsal tegmental nucleus, and the locus coeruleus [194]. The hippocampus plays a role in memory for context [197-205], context specific encoding [206, 207] and retrieval [207-209], episodic memory consolidation and retrieval [156, 210, 211] as well as the storage of emotional memories through interactions with the amygdala [156].

Role in Extinction Learning

Previous research indicates that the hippocampus is an important neural substrate in extinction learning [206-209, 212-217]. For example, the extinction of conditioned appetitive responses to natural rewards [217], and drug-seeking behavior [218-221] involve various subregions of the hippocampus including the EC, subiculum and CA1. Hippocampal lesions impair the extinction of a conditioned response to stimuli previously paired with a natural appetitive reward (e.g., sucrose) [217]. Imaging studies suggest that a pathway between the vmPFC and left anterior hippocampus is necessary for the recall of a context-dependent extinction memory [216] and an enhancement of entorhinal projections to the hippocampus facilitates extinction recall and memory [135, 216]. Furthermore, Fuchs and colleagues have displayed that the dorsal hippocampus is an integral neural substrate that mediates contextual reinstatement of extinguished cocaine-seeking behavior [222].

Various molecular and biochemical processes within the hippocampus are associated with extinction learning. For example, activation of MAPKs [223], SRC tyrosine kinases [214], protein synthesis [56], NMDA receptors, and protein kinase A (PKA) [224] are necessary for the consolidation of extinction learning. Neuronal changes in activity have been observed in the CA1 and dentate gyrus regions of the hippocampus as a result of extinction training following cocaine self-administration [220]. Cocaine self-administration also enhances hippocampal LTP [225-227], which has been shown to persist into extinction following cocaine self-administration [228]. Maintenance of LTP in the hippocampus 10 days post-extinction of cocaine self-administration was nearly identical to LTP in the hippocampus of cocaine self-administering animals suggesting that neuronal changes in the brain due to cocaine use may facilitate long term changes in the hippocampus.

Diminishing or reversing these changes may be necessary for facilitating the extinction of drug-associated memories and behaviors [228].

THE DORSAL AND VENTRAL STRIATUM

Functional Role and Anatomical Connectivity

The striatum is divided into a dorsal and ventral section. Both sections have observable anatomical subdivisions. The dorsal striatum is comprised of the caudate and putamen while the olfactory tubercle and Acb make up the ventral region. The Acb is located where the head of the caudate and anterior portion of the putamen meet. It is often divided into the AcbC and AcbSh. The striatum is the primary input zone of the basal ganglia. Afferent projections are received from a number of different brain regions including the PFC, amygdala, VTA, hippocampus, GP, and subthalamic nucleus [229-232]. Efferent signals are first mediated by the ventral pallidum and passed on to the dorsomedial thalamus and PFC [230].

As part of the extrapyramidal motor system and the largest component of the basal ganglia, the striatum is well known for the pivotal role it plays in mediating different aspects of reward [161, 180, 233]. Striatal subregions are also involved in multiple facets of learning and memory, including appetitive conditioning and instrumental learning [65, 234-237]. Furthermore, the striatum is involved with motor control, action selection, habit learning, and various other cognitive processes involving executive function [238, 239].

Role in Extinction Learning

Recent evidence suggests that the striatum may mediate extinction learning [137, 240]. Unfortunately, conflicting results from inactivation studies have provided different hypotheses regarding the striatum's role in extinction [241-243]. For instance, lesions to the Acb have been shown to facilitate [241] but also inhibit extinction [242, 243] of instrumental responding to natural rewards.

Clearly, striatal subregions are an important subcomponent in mediating reward-related stimuli [180, 244, 245]. Following the presentation of unexpected rewards, reward-related stimuli [233, 245, 246], and aversive stimuli [247, 248], functional magnetic resonance imaging (fMRI) studies show that there is an increase in striatal activity. Dopaminergic neurons projecting from the midbrain to the striatum have been implicated in responses to novel stimuli [249, 250], unexpected rewards [244, 251] and aversive stimuli [252] and may underlie the prioritizing of salient stimuli through a reallocation of brain resources [238]. Specifically, dopaminergic innervation from the ventral midbrain to Acb has repeatedly been shown to be involved in the primary rewarding and reinforcing effects of various drugs of abuse (see [253, 254] for recent reviews). On the other hand, dorsal regions [219] appear to play a key role in the transition from casual to compulsive drug use [10, 210, 255, 256]. Here, glutamatergic substrates are believed to be necessary for cue-controlled cocaine-seeking behavior [257]. Finally, it is worth noting that inactivation of dorsal regions blocks cue-induced reinstatement of cocaine-seeking behavior [258] while the inhibition of extracellular signal-regulated kinase (ERK) in the AcbC region results in a lasting attenuation of drug-induced reinstatement of cocaine conditioned place preference as well as cocaine-induced phosphorylation of several signaling molecules including ERKs, cAMP response element binding, Elk-1 and fos [259].

Extinction training involves a number of neurochemical and molecular processes in the striatum [240, 249, 260-262]. As such, there is evidence that extinction procedures following cocaine self-administration produce various hallmarks of neuronal plasticity in the Acb [258, 262]. For example, extinction training restores cocaine-induced deficits in tyrosine hydroxylase immunoreactivity in the AcbSh [262]. On the other hand, these investigators found that animals not undergoing extinction training showed a persistent reduction in levels of the enzyme following cocaine self-administration [262]. At the same time, other research has shown that cocaine-induced deficits in levels of the NR1 subunit of the NMDA receptor in the AcbC are normalized after extinction training [261]. Extinction training also induces an upregulation in the expression of the GluR1 and GluR2/3 subunits of the AMPA receptor in the Acb [240, 260], and virally-mediated upregulation of these AMPA subunits in this region facilitates extinction learning [240]. Consistent with this, GluR1 deletion in mice results in resistance to extinction following cocaine or food self-administration [263]. These lines of evidence show a considerable amount of neuroplasticity in the Acb during extinction learning of drug-associated memories and thus may serve as a novel therapeutic site for the treatment of drug addiction.

CONCLUSION

Learning and memory processes have been hypothesized to underlie drug addiction [1, 5]. Many common neural mechanisms exist between mnemonic systems and drug-addiction making a greater understanding of the neurobiological mechanisms underlying extinction of drug-related memories and behaviors an essential task for future research. While it is clear that drug-associated cues can elicit craving and therefore serve as an obstacle to treatment, they also provide a potential site for the development of novel therapeutics for addiction The majority of research examining the neurobiological mechanisms of extinction learning have centered on non-drug rewards or aversive conditioning, but recent studies have emerged indicating that the PFC, amygdala, hippocampus and striatum are important components that mediate the extinction of drug-associated memories and behavior [81, 190, 220, 228, 240, 258, 260, 262].

The extent to which pathways among these structures interact to mediate extinction learning is not fully understood but recent evidence provides multiple candidate regions (see [136] for a review) including, PrLC projections to the basal nucleus of the amygdala, LA, and CE mediating the expression of conditioned fear [264]. Conversely, projections from the ILC excite GABAergic neurons in the intercalated [265] cell masses inhibiting the CE thereby promoting the extinction of conditioned fear [266]. The expression of cocaine- and heroin- seeking behavior involves projections from the PrLC to the AcbC [267-272], whereas projections from the ILC to the AcbSh mediate the extinction of cocaine-seeking behavior [137].

Clearly, more research is needed for determining the complex interactions among these structures, including hippocampal and striatal connections possibly mediating the extinction of drug-associated memories. Elucidation of the neural mechanisms underlying extinction learning of drug-related memories depends on sophisticated novel experimental methods in order to truly understand the neuroanatomical structures underlying the formation and extinction of memories related to drug addiction. Future research should also examine the influence of different neurotransmitter systems on extinction learning. For example, within the PFC, activation of the cannabinoid CB1 receptors facilitates the extinction of conditioned fear whereas inhibition of the same receptor attenuates extinction of conditioned fear [266]. Determining the role and amount of impact that agonists acting at CB1, glutamate, or GABA receptor sites have on the extinction of drug-associated memories may help answer important questions regarding the neuroanatomical circuits underlying the extinction of drug-associated memories.

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ABBREVIATIONS

Acb = Nucleus accumbens

AcbSh = Nucleus accumbens shell

ACC = Anterior cingulate cortex

AMPA = α-Amino-3-hydroxyl-5-methyl-4-isoxazole-propionate

BLA = Basolateral amygdala

CA1 = Cornu ammonis 1

CA2 = Cornu ammonis 2

CA 3 = Cornu ammonis 3

CA4 = Cornu ammonis 4

CCK = Cholecystokinin

CPP = Conditioned place preference

CPP = 3-(+-)2-Carboxypiperazin-4yl propel-1 phosphate

CPu = Caudate-putamen

CRF = Corticotropin releasing factor

CS = Conditioned stimulus

DCS = D-cycloserine (D-4-amino-3-isoxazolidone)

DG = Dentate gyrus

dmPFC = Dorsomedial prefrontal cortex

EC = Entorhinal cortex

fMRI = Functional magnetic resonance imaging

GABA = Gamma-Aminobutyric acid

GP = Globus pallidus

ILC = Infralimbic cortex

IVSA = Intravenous drug self-administration

lOFC = Lateral orbitofrontal cortex

LTD = Long-term depression

LTP = Long-term potentiation

MAPK = Mitogen-activated protein kinase

mOFC = Medial orbitofrontal cortex

mPFC = Medial prefrontal cortex

NMDA = N-methyl-D-aspartate

NPY = Neuropeptide Y

OFC = Orbitofrontal cortex

PFC = Prefrontal cortex

PI-3K = Phosphatidylinositol 3-kinase

PKA = Protein kinase A

Pir = Piriform cortex

PrLC = Prelimbic cortex

US = Unconditioned stimulus

vmPFC = Ventromedial prefrontal cortex

VTA = Ventral tegmental area

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