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Perspective

The Role of Acetylcholine in Cocaine Addiction

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Central nervous system cholinergic neurons arise from several discrete sources, project to multiple brain regions, and exert specific effects on reward, learning, and memory. These processes are critical for the development and persistence of addictive disorders. Although other neurotransmitters, including dopamine, glutamate, and serotonin, have been the primary focus of drug research to date, a growing preclinical literature reveals a critical role of acetylcholine (ACh) in the experience and progression of drug use. This review will present and integrate the findings regarding the role of ACh in drug dependence, with a primary focus on cocaine and the muscarinic ACh system. Mesostriatal ACh appears to mediate reinforcement through its effect on reward, satiation, and aversion, and chronic cocaine administration produces neuroadaptive changes in the striatum. ACh is further involved in the acquisition of conditional associations that underlie cocaine self-administration and context-dependent sensitization, the acquisition of associations in conditioned learning, and drug procurement through its effects on arousal and attention. Long-term cocaine use may induce neuronal alterations in the brain that affect the ACh system and impair executive function, possibly contributing to the disruptions in decision making that characterize this population. These primarily preclinical studies suggest that ACh exerts a myriad of effects on the addictive process and that persistent changes to the ACh system following chronic drug use may exacerbate the risk of relapse during recovery. Ultimately, ACh modulation may be a potential target for pharmacological treatment interventions in cocaine-addicted subjects. However, the complicated neurocircuitry of the cholinergic system, the multiple ACh receptor subtypes, the confluence of excitatory and inhibitory ACh inputs, and the unique properties of the striatal cholinergic interneurons suggest that a precise target of cholinergic manipulation will be required to impact substance use in the clinical population.
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INTRODUCTION

Insights from animal models and neuroimaging studies have led to a greater understanding of the addictive process. Dopamine (DA) has been identified as the critical neurotransmitter in the reward circuitry mediating substance abuse and the primary focus of preclinical research and clinical treatment interventions (Adinoff, 2004; Di Chiara *et al*, 2004; Self, 2004). DA levels abruptly increase following the administration of many drugs of abuse, including cocaine, and cocaine is no longer self-administered in animal models of addiction following DA receptor blockade within the nucleus accumbens (NAc) (Chang *et al*, 1994). However, the addictive effects of cocaine are not entirely attributable to DA. For example, interventions augmenting DA activity have generally not been successful in significantly ameliorating cocaine use in cocaine-dependent populations (Kleber, 2003; Kosten *et al*, 2002). DA's contribution to the neurobiological etiology of cocaine addiction, therefore, is most likely shared with multiple other neurotransmitter systems (Arnold, 2005; Bardo, 1998; Gorelick *et al*, 2004; Kalivas, 2004; Muller *et al*, 2003; Roberts, 2005).

Drug addiction has been described as a disease of the brain reward system wherein drugs activate the neuronal circuitry involved in reward and memory (Dackis and O'Brien, 2001). This activation produces an aberrant engagement of the learning process (Hyman, 2005). Because of the effect of cholinergic systems on reward and drug self-administration, the prevalence of acetylcholine (ACh) within the striatum (Butcher and Butcher, 1974; Pisani *et al*, 2001), and the involvement of ACh in higher order cognitive processes (Pepeu and Giovannini, 2004), ACh may play an important role in the addictive processes underlying cocaine dependence. To date, research has emphasized the role of ACh in neurocognitive disorders, such as Alzheimer's and Parkinson's disease (Bosboom *et al*, 2003; Mesulam, 1996), as well as nicotine dependence (Stolerman and Shoaib, 1991), with less attention devoted to the role of ACh in other addictive disorders.

This review will present and integrate the research on the role of ACh in cocaine dependence. We will initially provide an overview of the animal models of addiction described in

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this review, followed by an overview of the ACh system, highlighting aspects that are central to this paper. A discussion of the effects of reward, including cocaine, on mesostriatal ACh will follow. This will be coupled with a description of the effects of cholinergic perturbations on cocaine self-administration, reinforcement, and sensitization, as well as the effects of chronic cocaine administration on ACh receptors. The balance of the review will examine the role of hippocampal, striatal, amygdalar, and prefrontal ACh in various cognitive aspects of addiction, including learning, attention, and executive functioning, as these processes are believed to be crucial to the long-term maintenance of cocaine dependence. The brain regions associated with each aspect of the review are described and, where applicable, relevant neurobiologic disruptions in addicted subjects are discussed. The review concludes with a brief discussion of the potential of ACh as a target of pharmacological treatment intervention and future directions of study. A table (Table 1) provides a summary of the key conclusions and references described in this review.

OVERVIEW OF ANIMAL MODELS OF ADDICTION

Various animal model paradigms have been utilized in elucidating the role of ACh in addiction, most notably self-stimulation, self-administration, drug reinstatement, and conditioned place preference (CPP) (O'Brien and Gardner, 2005; Sanchis-Segura and Spanagel, 2006). In self-stimulation studies, experimental animals perform an operant response to electrically stimulate a specific brain region (Olds and Milner, 1954). Positioning the electrode within the ventral tegmental area (VTA) or DA projections (mesostriatal pathway) to the NAc produces the most reliable intracranial self-stimulation (ICSS) response rate (Wise, 1996). The most commonly used ICSS method is the curve shift paradigm (Miliaressis *et al*, 1986). By altering the ICSS current, the resulting response rate curve resembles the traditional dose–response curves obtained in pharmacology. The drug effects on reinforcement can then be estimated by comparing ICSS curves from saline and drug sessions. Within the mesostriatal pathway, DA agonists increase the effects of the ICSS reinforcers and produce the same response rate with lower ICSS current values (leftward shift), while DA antagonists have the opposite effect (Miliaressis *et al*, 1986).

In self-administration studies, animals are trained to perform a response (eg lever press or nose poke) that results in administration of the drug being studied. The reinforcing qualities of the drug are gauged by varying the number of responses required to obtain a drug dose. The more responses an animal provides to obtain a drug, the more reinforcing the drug (Gardner, 2000; Jacobs *et al*, 2003). Fixed ratio (FR) models of reinforcement are often used to assess drug effects. In FR models, animals increase their rate of self-administration as the unit dose of a drug is decreased (to compensate for decreases in the unit dose) and reduce responding as the unit dose is increased (Arnold and Roberts, 1997; Koob, 2000). Progressive ratio schedules are used to evaluate the reinforcing efficacy of a self-administered drug by increasing the response requirements for each successive reinforcement and determining the

Table 1 The Role of ACh in Cocaine Addiction: Summary of Findings (See Text for Details)

Process	Anatomical locus	Cholinergic function
Reward	VTA	ACh is rewarding at VTA (Ikemoto and Wise, 2002; Redgrave and Horrell, 1976)
		Rewarding effect of cocaine mediated through M_5 receptors (Fink-Jensen *et al*, 2003; Thomsen *et al*, 2005; Yeomans and Baptista, 1997; Yeomans *et al*, 2001)
	Striatum	Striatal ACh increase associated with reward, possibly satiation (Imperato *et al*, 1993a, b; Mark *et al*, 1992; Pratt and Kelley, 2004; Rada *et al*, 2005; Zocchi and Pert, 1994).
		Striatal ACh increase associated with cocaine acquisition (Berlanga *et al*, 2003; Crespo *et al*, 2006; Mark *et al*, 1999)
		Striatal ACh alters cocaine-induced locomotor sensitization (Heidbreder and Shippenberg, 1996; Hikida *et al*, 2001, 2003)
		mACh receptors decrease after chronic cocaine (Lipton *et al*, 1995; Macedo *et al*, 2004; Wilson *et al*, 1994; Zeigler *et al*, 1991)
	Amygdala	mAChR may facilitate acquisition of associative learning underlying context-dependent sensitization (Heidbreder *et al*, 1996; Itzhak and Martin, 2000)
Explicit memory	Hippocampus	ACh involved in the encoding of new information (Hasselmo and Fehlau, 2001; Hasselmo *et al*, 2002)
		Hippocampal ACh increases following cocaine use (Imperato *et al*, 1993a, b, 1996; Smith *et al*, 2004a, b)
Conditioned learning	VTA	VTA ACh involved in conditioned learning (Bechara and van der Kooy, 1989; Museo and Wise, 1994; Olmstead and Franklin, 1993) M_5-deficient rats decrease cocaine-induced CPP (Fink-Jensen *et al*, 2003)
	Striatum	Striatal ACh involved in conditioned learning (Legault *et al*, 2006)
		NAc ACh inhibits cocaine-induced CPP (Hikida *et al*, 2001, 2003)
		ACh antagonist blocks induction of locomotor sensitization to cocaine-induced CPP (Itzhak and Martin, 2000)
	Amygdala	Amygdalar ACh facilitates conditioned learning (McIntyre *et al*, 1998; Power *et al*, 2003)
		Amygdalar ACh alters cocaine-induced conditioned learning (See *et al*, 2003; Zeigler *et al*, 1991)
Attention	PFC	Elevated ACh may focus attentional resources toward salient stimuli (Baxter and Chiba, 1999; Robbins, 2002; Sarter *et al*, 2003) Cocaine-addicted subjects show impaired attention (Horner *et al*, 1996; Jovanovski *et al*, 2005)
Set shifting	PFC	ACh involved in set shifting (Ragozzino and Choi, 2004; Ragozzino *et al*, 2002)
	Dorsal striatum	Deficits in dorsal striatal ACh activation may contribute to reversal learning deficits (no direct evidence to date) (Ragozzino and Choi, 2004; Ragozzino *et al*, 2002; Chen *et al*, 2004)
		Cocaine-addicted subjects show impaired set shifting (Ardila *et al*, 1991; Beatty *et al*, 1995; Rilling and Adinoff, 2007; Rosselli *et al*, 2001)

breaking point at which the animal will no longer respond (Arnold and Roberts, 1997; Koob, 2000). Increasing the unit dose of drug self-administration increases the breaking point on a progressive schedule. Another factor to consider in interpreting results is the effect of the inverted U-shaped dose–response curve on responding (Koob, 2000). A decrease in the number of reinforcements obtained may reflect either a decrease or an increase in the drug's reinforcing effects, depending on the doses of drug chosen for study.

In reinstatement models, the extinction of drug self-administration is followed by re-exposure to experimenter-administered drugs, drug-associated stimuli, or stressors. These procedures reinstate the drug-seeking behaviors that previously resulted in drug administration (eg lever press). This paradigm has been widely applied to assess the psychological and neurobiological mechanisms of relapse (Katz and Higgins, 2003; Schindler *et al*, 2002; Shaham *et al*, 2003). In the CPP paradigm, the rewarding properties of a compound are associated with the particular characteristics of a given environment (Bardo *et al*, 1995; Schechter and Calcagnetti, 1993). After conditioning, the animal spends more time in the environment associated with the rewarding drug. When the CPP paradigm is used in the context of sensitization, animals experience a greater drug effect in a previously conditioned, *vs* a novel, location (Robinson *et al*, 1998; Stewart and Vezina, 1988).

Useful strains of mice (ie 'knockout mice') have also been developed by genetically disrupting drug targets (receptors and transporters) or proteins in the target's pathway (Balster, 1991). Although most of the referenced studies are *in vivo* by design, *in vitro* studies have also been used to isolate various biological mechanisms from the living organism (Bolanos *et al*, 2000, 2002; Vanderschuren *et al*, 1999).

OVERVIEW OF THE CENTRAL CHOLINERGIC SYSTEM

Central nervous system (CNS) cholinergic neurons arise from multiple discrete sources, projecting to specific brain regions with well-defined cognitive, affective, and behavioral functions. Within the CNS, ACh is involved in motor behaviors, modulating the behavioral states associated with incoming information such as emotional tone, motivation, and arousal (Mesulam, 1996), as well as complex cognitive processes such as attention, learning, and memory (Sarter *et al*, 2003). Limbic and paralimbic regions of the CNS contain the highest density of ACh innervations in the brain (Mesulam, 1996) and are thought to be most relevant to the process of addiction (Bonson *et al*, 2002; Childress *et al*, 1999; Goldstein and Volkow, 2002). These regions include the ventral striatum (including the NAc), dorsal striatum, VTA, substantia nigra (SN), amygdala, hippocampus, and prefrontal cortex (PFC) (Lautin, 2001; Papez, 1995).

Muscarinic and Nicotinic ACh Receptors

The effects of ACh are mediated by muscarinic (mAChR) and nicotinic (nAChR) receptors. mAChRs are slow-acting, G-protein-coupled receptors that mediate their responses by activating a cascade of intracellular pathways. Activation of mAChRs by an applicable agonist causes a prolonged reduction of potassium conductance, inducing heightened cortical receptivity to other excitatory input (Wess, 1993). In contrast, nAChRs are fast-acting, ligand-gated ion channels that, upon binding with ACh, open to allow the diffusion of cations (Mihailescu and Drucker-Colin, 2000).

Molecular cloning studies have revealed the existence of five distinct mAChR subtypes (M_1–M_5). These receptors are widely expressed throughout the central and peripheral nervous system (Wess, 1993). M_1, M_2, and M_4 AChRs are mainly present in forebrain regions, while M_3 and M_5 receptors are distributed throughout the brain (Bonner *et al*, 1987; Levey, 1996). M_1, M_3, and M_5 (M_1-like) receptors are coupled to G_q proteins that activate phospholipases. In contrast, M_2 and M_4 receptors (M_2-like) are coupled to G_i proteins and inhibit adenylyl cyclase. Within the mesostriatal pathway, M_5 receptors are primarily found in the midbrain (Weiner *et al*, 1990), whereas M_1 and M_4 (and some M_2) are in the striatum (Levey *et al*, 1991). Neuronal nicotinic receptor subtypes include α and β subunits loosely categorized as two types: α–β subunit combinations (α_2–α_6, α_{10}, and β_2–β_4) and homo-oligomeric combinations (α_7–α_9). Of the former group, $\alpha_2\beta_4$ are the most common subunits and are widely expressed in the mammalian brain, including the dopaminergic midbrain and striatal regions. Of the latter group, only the α_7 subunit is widely distributed in the mammalian brain (Graham *et al*, 2002; Zhou *et al*, 2003).

ACh Interneurons and Limbic Pathways

ACh interneurons are the primary source of ACh to the dorsal and ventral striatum (Calabresi *et al*, 2000; Pisani *et al*, 2001; Zhou *et al*, 2002). These interneurons integrate a variety of cognitive, limbic, and motor information (Tisch *et al*, 2004) and undergo plasticity and learning, which, in turn, influences striatal output signaling (Aosaki *et al*, 1994). In addition to striatal interneurons, eight discrete ACh neuronal pathways innervate the functional subdivisions of the human cerebral cortex and subcortical structures of the CNS (Mesulam, 1996). Three of these pathways are particularly relevant to this discussion (see Figure 1): (1) the mesopontine nuclei (comprised of the pedunculopontine and laterodorsal tegmental nuclei) of the rostral brainstem, which provides ACh innervations to the VTA, SN, and thalamus (Mena-Segovia *et al*, 2005); (2) the nucleus basalis of Meynert (NBM), which provides the principal ACh input to the cerebral cortex and amygdala (Mesulam, 1996); and (3) the medial septal-diagonal band of Broca, which provides primary ACh input to the hippocampus (Lewis and Shute, 1967). For purposes of this review, the NBM and medial septal-diagonal band are at times collectively referred to as the basal forebrain.

MESOSTRIATAL ACETYLCHOLINE AND REWARD MEDIATION

The reward system is engaged in basic survival functions such as hunger, thirst, and sexual arousal (Hyman, 2005; Shizgal *et al*, 2001). These motivational states increase the

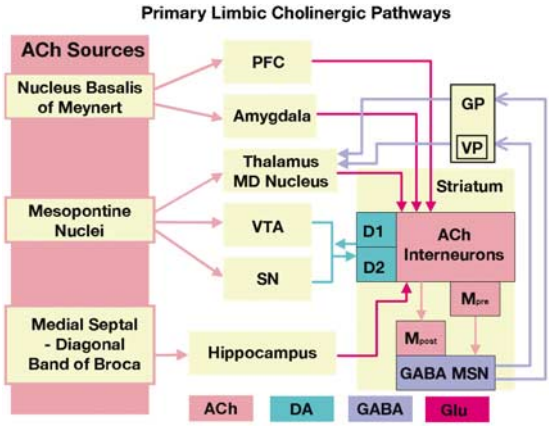

Figure 1 Limbic and paralimbic regions contain the highest density of acetylcholine (ACh) innervations in the brain. The three primary sources of cholinergic input are (1) the mesopontine nuclei (comprised of the pedunculopontine and laterodorsal tegmental nuclei), which provide ACh innervations to the VTA, SN, and thalamus, (2) the nucleus basalis of Meynert (NBM), which provides the principal ACh input to the cerebral cortex and amygdala, and (3) the medial septal-diagonal band of Broca, which provides primary ACh input to the hippocampus. Striatal ACh interneurons are largely influenced by dopamine (DA) receptors D_1 and D_2. Striatal muscarinic ACh interneurons primarily consist of M_1, M_2, and M_4; M_1 is post-synaptic (M_{post} in the figure) and excitatory whereas M_2 and M_4 are pre-synaptic and inhibitory (M_{pre} in the figure). These interneurons synapse with γ-aminobutyric acid (GABA) medium spiny output neurons (MSNs). The ventral striatum, central to the motivations and reward behaviors that underlie drug addiction, projects output neurons to the ventral pallidium (VP) of the globus pallidus (GP) and, in turn, to the mediodorsal (MD) nucleus of the thalamus. The dorsal striatum, involved in the motor processes and conditioned learning of drug addiction, sends projections either directly or indirectly (via the external globus pallidus and subthalamic nucleus) to the internal segment of the globus pallidus and pars recticula of the substania nigra. The GP further projects, through GABAergic neurons, to the mediodorsal (MD) nucleus of the thalamus. Glutaminergic neurons from the MD project to the prefrontal cortex (PFC). Synaptic communication within the reward circuit is conducted via DA (modulatory), acetylcholine (ACh, modulatory), glutamate (GLU, excitatory), and γ-aminobutyric acid (GABA, inhibitory) neurotransmission.

salience of the goal objects (food, water, sexual partner), increasing the likelihood that these rewards are actively sought (Kelley and Berridge, 2002). Like natural rewards, addictive drugs, such as cocaine, stimulate the reward pathway and produce subjective feelings of pleasure. However, when drugs of abuse are repeatedly used, behaviors related to sustaining the addiction may progressively supplant behaviors optimal for survival. This single-minded pursuit tends to undermine, rather than promote, species survival, effectively 'hijacking' the neural systems related to the pursuit of rewards (Hyman *et al*, 2006).

The rewarding effects of natural reinforcers and addictive drugs, including cocaine, are related to their ability to activate the mesolimbic circuit in the midbrain VTA and stimulate the release of DA within the shell compartment of the NAc (Caine *et al*, 1997; Wise and Rompre, 1989). Drugs that facilitate DA transmission within the mesolimbic pathway enhance the processes by which otherwise neutral stimuli acquire incentive salience and motivate further drug-seeking behavior (Berridge and Robinson, 1998; Wyvell and Berridge, 2000). Both natural rewards and addictive drugs initially stimulate the release of DA from the mesolimbic pathway. Cocaine elevates DA levels in the NAc by blocking DA transporter-mediated reuptake, prolonging the time that DA remains in the synaptic cleft. This results in increased synaptic concentrations of DA, which binds with post-synaptic DA receptors (Kupfermann *et al*, 2000). The DA response to a natural reward does not generally persist over time, as the organism rapidly habituates to these stimuli after a few exposures. Conversely, the response to addictive drugs is not influenced by habituation, as each drug administration stimulates the release of DA (Bradberry *et al*, 2000; Di Chiara *et al*, 2004; Lecca *et al*, 2007). In addition, the DA response of addictive substances is several fold higher than that elicited by novel, naturally occurring rewards (Di Chiara *et al*, 1999).

Mesostriatal Cholinergic Neurons

ACh projections from the laterodorsal tegmental nucleus of the pons activate VTA DA neurons via ACh receptors. Both muscarinic, particularly M_5 (Weiner *et al*, 1990), and nicotinic (Clarke and Pert, 1985) receptors provide input into VTA dopaminergic neurons (DANs). In turn, afferent DA projections from the VTA enervate the shell compartment of the NAc and activate ACh striatal interneurons, initiating the release of ACh. In the striatum, M_1, M_2, and M_4 receptor subtypes predominate, whereas M_3 and M_5 subtypes are barely detectible (Weiner *et al*, 1990). The striatal cholinergic interneurons are physically large but make up less than 5% of the striatal neurons (the others being GABAergic medium spiny neurons (MSNs) and GABAergic interneurons) and function through both direct synaptic transmission and volume transmission (spillover) (Koos and Tepper, 2002). Striatal ACh interneurons are tonically active neurons (TANs); these neurons exhibit a transient depression of tonic firing in response to both rewarding and aversive environment events and are influenced by past experience (Apicella, 2007). Specifically, these interneurons appear highly responsive to stimulus detection, movement control, and context recognition. Thus, while TANs are somewhat responsive to the experience of rewards, they exhibit a significantly greater response to contextual features (cues) associated with the reward (Aosaki *et al*, 1994; Apicella *et al*, 1997; Kimura *et al*, 2003). This feature distinguishes the TANs from mesostriatal DANs, which are equally responsive to both rewards and their associated cues. In addition, TANs do not show a differential response based on reward probability whereas striatal DA activation reflects a mismatch between expectation and outcome (Morris *et al*, 2004). (These findings are best described for cholinergic interneurons in the dorsal striatum.) TANs synapse with striatal GABAergic MSNs. In contrast to the striatal ACh interneurons, the MSNs are physically active neurons (Apicella, 2002). The GABAergic MSNs project back to ACh interneurons and to basal forebrain ACh neurons (in addition to other regions), which, in turn, project to the cerebral cortex.

ACh and DA systems appear to coordinate striatal reward function in a feed-forward, complementary manner (Zhou *et al*, 2003). Striatal ACh is primarily controlled by VTA D_1-like (D_1, D_5) and D_2-like (D_2, D_3, D_4) receptors. Both D_1- and D_2-like receptors have been localized on the somata, dendrites, and axons of striatal cholinergic neurons

(Alcantara *et al*, 2003; Berlanga *et al*, 2005). Activation of the D_1 receptor subtypes stimulates, whereas that of D_2 receptor subtypes inhibits, striatal ACh release (Berlanga *et al*, 2005; Bertorelli and Consolo, 1990; Consolo *et al*, 1999; Drukarch *et al*, 1990; Stoof *et al*, 1987). Zhang *et al* (2002) have suggested that the offsetting action of the D_1 and D_2 receptor subtypes maintains the balance between ACh and DA. For example, whereas the dopaminergic stimulants cocaine and *d*-amphetamine and the D_1 agonist SKF 82958 increased ACh in the NAc shell and core, the selective D_1 SCH 39166 antagonist decreased accumbens ACh. The NAc ACh release induced by *d*-amphetamine, cocaine, and SKF 82958 was antagonized by SCH 39166, suggesting that D_1 exerts tonic stimulatory control (Consolo *et al*, 1999). However, in an elegant study in baboons utilizing positron emission tomography (PET), Ding *et al* (2000) assessed striatal nicotinic ACh output following the administration of D_1 and D_2 agonists (D_1: SKF 38393; D_2: quinpirole) and antagonists (D_1: SCH 23390; D_2: raclopride). Nicotinic receptor binding was determined using the selective ACh receptor ligand norchloro[^{18}F]fluoroepibatidine ([^{18}F]NFEP). Striatal [^{18}F]NFEP binding was increased following pretreatment with the D_2 agonist and decreased following pretreatment with the D_2 antagonist. Neither the D_1 agonist nor antagonist altered striatal [^{18}F]NFEP binding. Changes in striatal nicotinic AChR availability following D_2, but not D_1, agonist/antagonist challenges thus suggested that the D_2 receptors predominantly influence striatal nicotinic ACh output under physiological conditions. Using almost identical DA agonists (D_1: SKF 38393; D_2: quinpirole) and antagonists (D_1: SCH 23390; D_2: sulpiride)) as Ding *et al* (2000), Deng *et al* (2007) measured dopaminergic inhibition of hyperpolarization-activated cation current in striatal cholinergic interneurons. As observed in the non-human primate study (Ding *et al*, 2000), D_2 receptor, but not D_1 receptor, compounds modulated the firing of these TANs (Deng *et al*, 2007).

Striatal cholinergic output, in turn, modulates striatal DA efflux (see Zhang *et al*, 2002). M_4 receptors are often coexpressed with D_1 receptors (Ince *et al*, 1997; Weiner *et al*, 1990), although these two receptors may initiate opposing actions. Zhang *et al* (2002) explored the relative influence of various mAChRs on DA output by assessing the effects of oxotremorine (an mAChR agonist) in rats selectively bred as M_1, M_2, M_3, M_4, and M_5 deficients. The heightened efflux of DA induced by oxotremorine was unchanged in M_1- and M_2-deficient mice. M_4 receptor-deficient mice demonstrated an absence of striatal DA output following oxotremorine, suggesting that M_4 exerts a stimulatory effect on DA release. In contrast, M_3-deficient mice showed an increase in DA release following oxotremorine, indicating that M_3 receptors exert an inhibitory effect on DA. DA and ACh modulation is further enhanced by the distinct differences noted earlier in the specific stimuli that provoke striatal DA (DANs) and ACh (TANs) signaling (see Cragg, 2006).

Additional influences of striatal ACh include mAChRs located on striatal MSN output neurons. The MSNs induce the release of inhibitory neurotransmitter γ-aminobutyric acid, further promoting striatal signaling (see Figure 1). Harsing and Zigmond (1998) found that striatal GABAergic outflow is under the influence of M_1 stimulatory and M_3 inhibitory, but not M_2, receptors, and Santiago and Potter (2001) have reported that M_4 receptors are also highly expressed on GABAergic projection neurons. ACh also directly influences glutaminergic and GABAergic effects on midbrain DA neurons, further effecting striatal DA release (Grillner *et al*, 2000). High concentrations of mGlu2 receptors on striatal cholinergic neurons (Pisani *et al*, 2002), mediated through M_2 and M_3 receptors, reduce striatal glutaminergic release (Sugita *et al*, 1991). Serotonergic fibers from the raphe nucleus also demonstrate a potent excitatory effect on striatal cholinergic interneurons (Bonsi *et al*, 2007). Thus, as will become increasingly apparent in the following section, a myriad of inhibitory and excitatory DA and ACh receptor subtypes, coupled with complicated feedback interactions, result in relatively complex and at times inconsistent effects of either endogenous or exogenously administered ACh.

Non-dopaminergic Effects of Cocaine on ACh

Throughout this review, it will generally be presumed that the effects of cocaine on the cholinergic system are primarily mediated through dopaminergic efflux. Other direct interactions, however, may be in play. Cocaine has direct effects on both M_1 and M_2 (Flynn *et al*, 1992; Karpen and Hess, 1986; Sharkey *et al*, 1988), as well as nicotinic (Niu *et al*, 1995; Swanson and Albuquerque, 1987), cholinergic receptors. Cocaine also acts as a powerful local anesthetic through a direct effect on voltage-gated sodium channels. Recent work by Cooper *et al* (2006) suggests that the effect of cocaine on sodium channels in the subiculum may alter cocaine reinstatement. Both preclinical (DC Cooper *et al*, unpublished observation) and clinical (Adinoff *et al*, 2001) studies further suggest that neural activation by other sodium channel-mediated local anesthetics (ie procaine, lidocaine) is an attenuated effect following chronic cocaine administration. Thus, the effect of cocaine on cholinergic systems discussed below may be affected by non-dopaminergic processes, including a direct effect on ACh receptors.

Generalized Effects of the Cholinergic System on Reward and Drug Taking

Systematically administered cholinomimetics or cholinesterase inhibitors generally induce depressive-like behaviors, including learned helplessness. Antimuscarinic drugs reverse these behaviors and can produce euphorigenic-like effects (Janowsky and Overstreet, 2000; Lucki, 1997; Porsolt *et al*, 1978). Therefore, it might be predicted that compounds that increase cholinergic activity would decrease the rewarding effect of drugs. Consistent with this formulation were early observations that physostigmine, an acetylcholinesterase (AChE) inhibitor, decreases cocaine self-administration in rhesus monkeys (de la Garza and Johanson, 1982). On the other hand, rhesus monkeys trained to self-administer cocaine decreased their intake when administered atropine, an mAChR antagonist (Wilson and Schuster, 1973). Since physostigmine promotes ACh elevations both at mACh and nACh receptors, these studies may suggest that the mACh and nACh systems have opposing effects. In addition, physostigmine and atropine

have significant generalized adverse effects that could effect responding. However, as detailed below, these inconsistencies persist when considering regionally specific alterations in mAChR systems in more recent, and far more extensive, preclinical studies.

VTA Acetylcholine and Reward

ACh agonists are rewarding when injected into the VTA. ACh infusions into the VTA potentiate ICSS (Redgrave and Horrell, 1976) and the ACh agonist carbachol and the AChE inhibitor neostigmine (which increases ACh concentrations) are both self-administered into the VTA (Ikemoto and Wise, 2002). M_5 receptor-deficient ($M_5^{-/-}$) rats lack sustained NAc DA release following electrical stimulation of VTA cholinergic input (Forster *et al*, 2002), and striatal DA release induced by oxotremorine is significantly reduced in these M_5 receptor-knockout mice (Zhang *et al*, 2002). The absence of M_5 receptors on the VTA likely accounts for the lower rate of cocaine self-administration in $M_5^{-/-}$ rodents (Fink-Jensen *et al*, 2003; Thomsen *et al*, 2005). Although $\alpha_{4-6}\beta_2$ and $\alpha_{4-5}\beta_2$ nAChRs have been identified on VTA DANs (Klink *et al*, 2001), VTA mACh receptors appear to play a more prominent role in maintaining reward relative to nAChRs. Using lateral hypothalamic brain stimulation as the reward, Yeomans and Baptista (1997) found that the intra-VTA administration of an mAChR antagonist (atropine) produced a rightward shift in the dose–response curve of self-stimulation (signaling slower rates of responding at a given dose) four-fold greater than that of two nAChR antagonists (mecamylamine and dihydro-beta-erythroidine (DHβE)). However, Smith *et al* (2004b) did not find a significant difference in VTA ACh concentrations in rats administered cocaine, either by self-administration or yoked, relative to yoked saline rats. Overall, the literature suggests that VTA ACh is rewarding, mediates the rewarding effects of cocaine and other positive reinforcers, and is primarily regulated by M_5 receptor subtypes.

Striatal Acetylcholine and Reward

Striatal ACh increases following nonspecific, appetitive rewards. Mark *et al* (1992) reported an increase in extracellular NAc ACh following both feeding and water intake (following 20-h food or water deprivation, respectively). In a separate experiment, monitoring of NAc ACh at 10-min intervals during free-feeding revealed an increase in ACh immediately following maximal food intake (Mark *et al*, 1992). Rada *et al* (2005) also demonstrated a significant increase of ACh in the NAc shell following binging in 'sucrose-dependent' rats. Unlike the relatively quick increase in ACh observed by Mark *et al* (1992), Rada *et al* (2005) reported a maximal ACh after the sucrose meal ended. The involvement of NAc ACh in food reward appears to be mediated by mAChR, as the administration of scopolamine (1.0 or 10.0 μg/side) into the NAc core or shell inhibited both the appetitive learning and the number of lever presses expended for the sucrose, whereas mecamylamine (10.0 μg/side) did not (Pratt and Kelley, 2004). In a follow-up study, Pratt and Kelley (2005) reported that both ventrally and dorsally administered scopolamine into the striatum (0.5 or 10.0 μg/bilaterally) reduced 24-h food intake without affecting water intake.

Similar to elevations in VTA ACh concentrations following cocaine and striatal ACh concentrations following food intake, striatal elevations in ACh have also been associated with drug administration. Following a single dose of 10 and 20 mg/kg i.p. cocaine, for example, Imperato *et al* (1993a) found a 51 and 80% increase, respectively, in caudate nucleus ACh. Zocchi and Pert (1994) reported an increase in striatal ACh following 20 and 40 mg/kg i.p. cocaine, but not 10 mg/kg, and Mark *et al* (1999) also found an increase in shell NAc ACh in rats receiving yoked cocaine relative to those receiving saline. A similar finding in cocaine-infused rats, compared to saline-infused controls, was reported by Smith *et al* (2004b) in ACh turnover of the caudate putamen, but not the NAc. Additionally, Smith *et al* (2004b) found no significant differences in ACh concentrations of either region following 20 days of yoked cocaine infusion. Striatal increases in ACh following cocaine and *d*-amphetamine were blocked with the D_1 antagonists SCH 39166 and SCH 23390 (Consolo *et al*, 1999; Imperato *et al*, 1993a), indicating that striatal increases in ACh were mediated by stimulant-induced increases in DA. In rats self-administering alcohol relative to yoked controls, Zocchi and Pert (1994) reported a similar dose-dependent increase in striatal ACh following morphine and a 51% increase in cyclin-dependent kinase 5 immunoreactivity, a measure of neuronal plasticity, in NAc shell cholinergic neurons (Camp *et al*, 2006). However, other investigators have found that the NAc dopaminergic efflux that follows the acute and/or chronic administration of ethanol (Rada *et al*, 2004), diazepam (Rada and Hoebel, 2005), and morphine (Rada *et al*, 1991) is not paralleled by an elevation in striatal ACh.

ACh striatal efflux has also been associated with the acquisition of cocaine. Mark *et al* (1999) found that rodents self-administering cocaine for 14 consecutive days significantly increased ACh release in the NAc shell more than rats non-contingently administered cocaine. Similarly, Crespo *et al* (2006) found that the run time (how fast an animal runs to obtain the contingent stimulus) was inversely correlated to ACh release in the NAc core during the acquisition of reminfentanil (a short-acting synthetic opioid) or cocaine (ie the shorter the run time, the greater the ACh release observed). Furthermore, acquisition of reminfentanil (cocaine was not tested) was blocked following the intra-accumbens administration of either scopolamine or mecamylamine (Crespo *et al*, 2006). Finally, Berlanga *et al* (2003) found a direct correlation ($R^2 > 0.90$) between the percent of cholinergic neurons activated (as measured by Fos labeling) in the NAc shell and ventromedial striatum (but not the NAc shell or dorsolateral striatum) and the amount of cocaine self-administered in rats. Overall, these studies argue that cocaine, and possibly morphine and amphetamine, increases NAc ACh. Furthermore, the increase in ACh release appears to be positively correlated with the drug's positive reinforcing value. This striatal ACh elevation is likely a result of drug-induced D_1 stimulation. Furthermore, the rewarding experience of cocaine acquisition is also associated with an elevation of striatal ACh.

The work of Smith *et al* offers a potentially contrasting view of the role of ACh in cocaine self-administration.

Smith *et al* (2004b) found that the NAc ACh turnover did not differ between cocaine self-administering rats (or yoked saline-infused rats) and yoked cocaine-infused rats, and that caudate putamen ACh was significantly lower in the self-administering rats relative to the yoked cocaine-infused rats. The different directions of findings by Smith *et al* (2004b) may be related to their use of pulse labeling to assess ACh turnover, as turnover rate measurements for ACh require short pulse times. Their findings, therefore, represent only the turnover of ACh during the pulse interval, which would not have assessed ACh turnover during cocaine's more extended duration of action. Smith *et al* (2004a) also bilaterally ablated cholinergic neurons in the posterior-NAc-ventral palladium in rats trained to self-administer cocaine. Ablation was performed with 192-IgG-saporin; 192-IgG-saporin is directed to cell-surface antigens that are expressed at high levels only on cholinergic neurons. Interneuron destruction induced a shift in the dose–intake relationship to the left, such that lesioned animals self-administered cocaine at doses below the pre-lesion threshold in a dose-related manner. This work suggests that the removal of ACh interneurons (decreasing ACh efflux) increased the rewarding effects of cocaine, which would seem to contrast with the aforementioned literature positively associating heightened striatal ACh to cocaine acquisition. The complicated interplay of striatal ACh with other receptor systems, as well as the myriad effects of the multiple cholinergic subtypes (including presynaptic inhibitory and postsynaptic excitatory receptors), makes it difficult to predict a specific direction of change in response to a generally destructive agent or a nonspecific agonist or antagonist.

Unlike ACh increases in VTA, however, there appears to be little evidence that striatal ACh is itself rewarding. In fact, striatal ACh is often associated with aversion. Aversive-related increases in striatal ACh are observed in response to the injection of a vehicle (Pfister *et al*, 1994), the conditioned stimulus of an aversive taste (Mark *et al*, 1995), and following inescapable automatic hypothalamic stimulation (Rada and Hoebel, 2001). When allowed to escape from the hypothalamic stimulation, extracellular ACh concentrations are significantly decreased (Rada and Hoebel, 2001). High levels of NAc ACh persist for up to 24 h following the Porsolt, or forced swimming, test following an early transient decrease (Rada *et al*, 2006). (The Porsolt test is a measure of 'behavioral despair,' or learned helplessness.) Microinjections of arecholine, a cholinergic agonist, into the NAc dose-dependently inhibit swimming in the Porsolt in rodents, and pirenzepine, an M_1 antagonist, increases swimming (Chau *et al*, 2001). Thus, increases in striatal ACh activation appear to heighten learned helplessness. Gallamine, an M_2 antagonist, also decreases swimming, presumably by blocking ACh autoreceptors and thereby increasing ACh concentrations (Chau *et al*, 2001). Hoebel and colleagues have also noted a dramatic increase in striatal ACh, relative to DA, concentrations during naloxone-induced morphine withdrawal (Rada *et al*, 1991), mecamylamine-induced nicotine withdrawal (Rada *et al*, 2001), flumazenil-induced diazepam withdrawal (Rada and Hoebel, 2005), naloxone-induced ethanol withdrawal (Rada *et al*, 2004), and following the presentation of a conditioned aversive stimulus in a taste aversion task (Mark *et al*, 1991, 1995). Electrophysiologic studies further reveal that the response of the cholinergic TANs differs following aversive stimuli relative to reward (Apicella, 2007).

Thus, there is now a substantial literature demonstrating a role of ACh in the acute administration of cocaine and the interpretation of its reinforcing effect. It remains unclear, however, exactly how ACh alters the perception of cocaine reinforcement. Rada and Hoebel (2000) have suggested a specific mechanism whereby NAc ACh has a satiating effect upon appetitive stimulus which complements the facilitatory effects of NAc DA. The interactive effects of DA and ACh then mutually contribute to produce a modulatory effect on other receptor systems. While there is evidence to support this interpretative, much of the above-referenced literature would be difficult to reconcile with this model.

Finally, the above section has used the term 'striatal' to describe a complex system comprised of multiple distinct regions with quite different functions. Although specific regions (ie NAc shell or core, caudate, putamen, dorsal striatum) were often noted, the referenced literature frequently did not isolate a more demarcated region. Given the different prescribed roles of the dorsal and ventral striatum (Gerdeman *et al*, 2003; White, 1996), it is presumed that the location of the ACh interneurons may have a significant effect on interpretation—although no such relationship was apparent in the reviewed studies. It is also noteworthy that the dorsal/ventral striatal distinction has recently come under question (suggesting a ventromedial *vs* dorsolateral distinction) (Voorn *et al*, 2004), further complicating any attempt to ascribe regional effects of striatal ACh. As noted previously, the excitatory and inhibitory effects of striatal ACh further complicate any generalized assumption of cholinergic effect and cocaine administration.

NEUROADAPTATION

ACh Receptor Alterations Following Cocaine

Persistent elevations in striatal ACh might be expected to produce a compensatory downregulation of striatal ACh receptors. Decreases in both mACh receptor density and K_d were, in fact, observed by Macedo *et al* (2004) following 7 continuous days of cocaine administration. Decreases in receptor density and dissociation constants were also identified with [^{3}H]-*N*-methylscopolamine at 30 min, 5 days, and 30 days following the cessation of cocaine administration (20 and 30 mg/kg). Zeigler *et al* (1991) also found a decrease of mACh receptors, as measured by quinuclidinyl benzilate binding, in both NAc and medial caudate regions following the implantation of a 5-day, slow-release pellet. Interestingly, a matched group of rats administered the same amount of cocaine over 5 days by daily, i.p. injections did not demonstrate similar reductions, suggesting that the rate of cocaine administration (continuous *vs* daily) significantly affects receptor disruption. Wilson *et al* (1994) reported a 26% reduction in mean NAc choline acetyltransferase (ChAT) (an enzyme that controls the production of ACh) activity in rat NAc immediately following the chronic, unlimited access to cocaine (approximately 90 mg/kg/day) (NAc (−32%), striatum (−18%)).

This reduction continued for 3 weeks (49 ± 5 days) (the last time point measured), suggesting a persistent compensatory decrease in ChAT in response to cocaine-induced elevations in striatal ACh. In contrast, Sousa *et al* (1999) reported an increase in both M_1-like (assessed with [^{3}H]-*N*-methylscopolamine in the presence of carbachol) and M_2-like (assessed with [^{3}H]-*N*-methylscopolamine in the presence of pirenzepine) mACh receptors following 7 days of cocaine administration (5 and 10 mg/kg), albeit at a lower dose of cocaine than that used by Macedo *et al* (2004). Finally, Lipton *et al* (1995) observed both an increase and a decrease in striatal mACh (assessed with [^{3}H]-quinuclidinyl benzilate) receptors following 5 days of cocaine administration, depending on whether measures were obtained 12 h, 2 days, or 21 days after the cessation of cocaine injections. *In toto*, these studies suggest a downregulation of the cholinergic system following cocaine administration and are consistent with an adaptive response to increased striatal cholinergic release during cocaine administration.

However, this literature is somewhat ambiguous, mirroring the more extensive literature assessing repeated cocaine administration on striatal D_1 and D_2 receptor density. Studies have variously reported receptor downregulation (Maggos *et al*, 1998; Zeigler *et al*, 1991), upregulation (Alburges *et al*, 1992, 1993; Macedo *et al*, 2004), and no alterations (Mayfield *et al*, 1992; Sousa *et al*, 1999) in D_1 densities between days 1 and 30 of withdrawal. Similar inconsistencies are reported with respect to D_2 receptors (upregulation (Macedo *et al*, 2004; Sousa *et al*, 1999; Zeigler *et al*, 1991); downregulation (Maggos *et al*, 1998; Volkow *et al*, 1993); no change (Alburges *et al*, 1992, 1993; Maggos *et al*, 1998)). Given the complex interplay between mesostriatal ACh and DA described earlier, it is perhaps not surprising that the extant literature is inconsistent with respect to the direction of striatal cholinergic change resulting from, or effecting, cocaine administration.

Cocaine-Induced Sensitization

Cocaine-induced sensitization in the VTA. Behavioral sensitization refers to the progressive increase in the locomotor stimulant properties of a drug following chronic drug administration and is considered a long-term neuro adaptation important for the maintenance of drug dependence (Kalivas *et al*, 1998; Robinson and Berridge, 1993; Vanderschuren *et al*, 1999). Cocaine-induced sensitization occurs through the stimulation of D_1 receptors on cortical afferents to the VTA, which, in turn, induces glutamate release. Glutamate activates ionotropic glutamate receptors located on DA neurons, triggering the long-term molecular adaptations that underlie sensitization (Kalivas, 1995). nAChRs are expressed on VTA neurons as well as cortical glutamate afferents to the VTA; β_2-containing nAChRs are expressed on DA and GABAergic neurons while α_7 nAChRs are primarily expressed on glutamatergic terminals (Klink *et al*, 2001). Both the heightened dopaminergic response and the psychomotor effects of cocaine-induced sensitization are prevented by mecamylamine, an nAChR antagonist that blocks both α_7- and β_2-containing VTA nAChRs (Schoffelmeer *et al*, 2002). Champtiaux *et al* (2006) have subsequently identified the VTA heteromeric β_2-containing nAChRs, but not homomeric α_7 nAChRs, as critical for the induction of cocaine-induced locomotor sensitization; intra-VTA microinjections of the $\alpha_4\beta_2$-selective containing antagonist DHβE, but not the α_7 antagonist methyllycaconitine, prevented the induction of behavioral sensitization to cocaine. On the other hand, Zanetti *et al* (2006) found that whereas the co-administration of DHβE and methyllycaconitine prevented sensitization to cocaine (as measured by extracellular DA release in the ventral striatum), neither antagonist was effective in preventing sensitization alone. Although differences in frequency and amount of cocaine dose and the interval following cocaine administration at which sensitization was assessed differed between the two studies, the reason for these distinctly different results is not readily apparent.

Cocaine-induced sensitization in the NAc. NAc mAChRs also exert an inhibitory influence on cocaine-induced behavioral sensitization (Wolf, 1998). Although Itzhak and Martin (2000) found no effect of scopolamine (1.0 mg/kg s.c.) on cocaine (20 mg/kg i.p.)-induced 'place-independent' sensitization, Hikida *et al* (2001) examined the role of accumbens ACh in cocaine-induced sensitization by ablating these interneurons with an immunotoxin-mediated cell targeting technique. Transgenic mice with bilateral ACh interneuron ablation displayed a prominent and progressive increase in locomotor activity at baseline and following daily cocaine administration (5, 10, and 20 mg/kg) relative to their wild-type littermates. Using the same technology, Hikida *et al* (2003) also reported that administration of the AChE inhibitor donepezil (which increases ACh synaptic concentrations) prior to cocaine administration (10 mg/kg, 3 days) blocked induction of locomotion sensitization to cocaine in rats. Furthermore, the AChE inhibitors donepezil and galanthamine also blocked hyperlocomotion after the establishment of locomotor sensitization (5 days, 10 mg/kg). This inhibition was abolished by ablation of the NAc cholinergic interneurons. Although the preceding studies suggest that ACh inhibits sensitization, Heidbreder and Shippenberg (1996) found that subcutaneously administered scopolamine blocked the induction, but not the expression, of cocaine-induced sensitization (20 mg/kg i.p., 5 days). Microinjections of the nicotinic antagonist DHβE into the NAc had no effect on cocaine-induced sensitized locomotor activity (Champtiaux *et al*, 2006).

Although mAChRs play an important role in VTA reward mediation, it appears that nAChR receptors are primarily involved in cocaine-induced behavioral sensitization in the VTA. In contrast, ACh exerts an effect on NAc cocaine-induced sensitization through mAChRs, although the direction of this effect is uncertain. As discussed below, striatal cholinergic activity also appears to heighten context-dependent locomotor sensitization.

ACETYLCHOLINE, LEARNING, AND MEMORY

Learning and memory are essential to the changes in behavior produced by addictive drugs. Drugs reinforce associations that initiate the storage of new information, strengthening neural pathways through synaptic plasticity and long-term potentiation (Calabresi *et al*, 2000; Everitt and Robbins, 2005; Hyman *et al*, 2006; Suzuki *et al*, 2001).

Acetylcholine is involved in both explicit and implicit memories, utilizing distinct neuronal systems.

Acetylcholine and Explicit Memory

Explicit memories (also called declarative memory) refer to the learning and memory of facts and events that require conscious recall (Tulving and Schacter, 1990). Explicit learning occurs within conscious awareness and with relatively little experience (Breese *et al*, 1989; Sharp *et al*, 1985). Through explicit memories related to drug use (ie, where the substance was obtained; where it was used; the social situation), as well as memories of the effects of the drug on internal affective states, the drug-addicted individual learns to manipulate the external environment to achieve desired affective states (Berke and Eichenbaum, 2001; Hirsh *et al*, 1979). Thus, this type of learning enables an individual to evaluate the outcome of their actions and to modify their future behavior accordingly, including either the induction of a hedonic state or the alleviation of an unpleasant affective state.

The locus of explicit memory is the hippocampus. The hippocampus contains among the highest concentrations of ACh in the CNS, and ACh is a critical component of hippocampal memory formation (Grecksch *et al*, 1978; Jaffard *et al*, 1980; Singh *et al*, 1974). Hippocampal ACh is projected from the septum and nucleus of the diagonal band (McKinney *et al*, 1983), and DA transmission at D_1 and/or D_2 receptors can enhance hippocampal ACh output (Imperato *et al*, 1993b). Drugs that block mAChRs, such as scopolamine, impair the encoding of new information (Hasselmo and Fehlau, 2001; Hasselmo *et al*, 2002) and depletion of ACh is linked to memory disorders such as Alzheimer's disease (Coyle *et al*, 1983; Quirion *et al*, 1989). Hippocampal ACh is theorized to facilitate the encoding of new information by simultaneously suppressing excitatory synaptic transmission and enhancing long-term potentiation, while leaving excitatory feed-forward synapses relatively unaffected (Hasselmo *et al*, 2002). ACh also modulates synaptic plasticity within the hippocampus (Colgin *et al*, 2003) and long-term potentiation is drastically reduced in genetically engineered mice lacking the mACh M_2 receptor (Seeger *et al*, 2004).

The acute administration of cocaine increases extracellular levels of ACh (Imperato *et al*, 1993a, 1996) and ACh turnover rates within the hippocampus (Robinson and Hambrecht, 1988). Enhancement of hippocampal ACh release induced by cocaine appears to occur through DA D_1 receptor activation, as ACh release was fully antagonized by the D_1 antagonist SCH 23390 (Imperato *et al*, 1993a; Robinson and Hambrecht, 1988). Cocaine-induced increases in hippocampal ACh are consistent with the downregulation of mACh receptor binding observed by Zeigler *et al* (1991) in rats continuously administered cocaine for 5 days (paradigm described earlier). On the other hand, Smith *et al* (2004b) found that a cocaine-yoked group of rats showed lower, not higher, concentrations of hippocampal ACh relative to a saline-yoked group. However, rats self-administering cocaine exhibited a significant elevation in both hippocampal ACh levels and ACh turnover relative to the cocaine-yoked group (Smith *et al*, 2004b), suggesting that the process of self-administering cocaine, and not the cocaine itself, is the critical component in increasing hippocampal ACh concentrations. Although these studies, *in toto*, are inconsistent with respect to the directional relationship between cocaine administration and hippocampal ACh release, they strongly suggest that changes in hippocampal ACh during investigator- and self-administration of cocaine may be involved in the solidification of hippocampal-mediated cocaine-related explicit memories. To our knowledge, however, this relationship has not been empirically confirmed.

Acetylcholine and Conditioned Learning

Implicit memory (also called nondeclarative memory) refers to the learning of perceptual and/or motor skills that usually follows repetition. These memories become reflexive once associations are formed, operating largely outside of awareness (Roediger, 1990; Schacter, 1992). Conditioned learning (also called associative learning), a type of implicit learning, is based on the principals of classical conditioning (Pavlov, 1927). Through this process, neutral stimuli acquire reinforcing qualities and motivational relevance, even in the absence of a drug. Since implicit memories are difficult to extinguish, they appear central to both the maintenance of cocaine addiction and relapse (Everitt and Robbins, 2005; White, 1996). This process forms the basis of drug-induced CPP and, relative to other types of conditioned learning, appears more difficult to extinguish. As there is an absence of habituation to drug-induced increases in DA (relative to natural rewards), the associations between the rewarding properties of cocaine and the related conditioned stimuli are continually strengthened with repeated use (Di Chiara *et al*, 2004). The NAc, amygdala, and basal forebrain all play a critical role in the development of conditioned learning following drug administration (Di Chiara *et al*, 1999; Everitt *et al*, 1999; Meil and See, 1997).

Conditioned learning and the VTA. CPP paradigms are most often used to assess the strength of associated stimuli with drug administration. The ACh agonist carbachol (Yeomans *et al*, 1985) and the nicotinic agonist cystisine (Museo and Wise, 1994) induce CPP when injected into the VTA. Conversely, lesions of the pedunculopontine nucleus (a source of ACh to the VTA) inhibit the development of CPP to morphine and amphetamine (Bechara and van der Kooy, 1989; Olmstead and Franklin, 1993). $M_5^{-/-}$ rodents also spend less time in a cocaine-paired compartment during a CPP procedure compared to wild-type rodents (Fink-Jensen *et al*, 2003). Consistent with the positive association of VTA ACh with reward, increasing both muscarinic and nicotinic cholinergic VTA activity appears to heighten CPP to drugs of abuse.

Conditioned learning and the striatum. Although ablation of cholinergic striatal neurons did not impair either contextual or cued fear conditioning in rats (Kitabatake *et al*, 2003), infusions of scopolamine into the dorsal striatum impaired the conditioned learning of a radial arm task when administered soon after training (Legault *et al*, 2006). With respect to cocaine, ablation of NAc cholinergic interneurons by an immunotoxin-mediated cell targeting

technique induced CPP for cocaine at much lower doses of cocaine than that in wild-type littermates (Hikida *et al*, 2001). The administration of AChE inhibitors (which increase ACh synaptic concentrations) also suppressed cocaine-induced CPP, and this effect was blocked by the ablation of ACh cells within the NAc (Hikida *et al*, 2003). These findings suggest that NAc ACh interneurons inhibit the associative learning that underlies cocaine addiction.

The association of a novel environment to stimulant administration has a profound effect on the development of behavioral sensitization (Browman *et al*, 1998; Crombag *et al*, 1996; Robinson *et al*, 1998). Seemingly in contrast to the findings described with CPP paradigms, Itzhak and Martin (2000) found that cocaine-induced place-dependent sensitization (context dependent), as measured by locomotor activity, was blocked by pretreatment with scopolamine (1 mg/kg s.c.). In this study, cocaine alone was administered for 5 consecutive days and produced a five-fold increase in locomotor activity. The administration of scopolamine 30 min prior to each cocaine injection completely abolished this increase. This is similar to findings described earlier, in which scopolamine (3 mg/kg s.c.) was observed to block the induction, but not the expression, of context-independent sensitized locomotor activity (Heidbreder and Shippenberg, 1996). However, Itzhak and Martin (2000) did not observe a disruptive effect of scopolamine on the induction of context-independent sensitization by cocaine, possibly due to the lower dose of scopolamine. Although these studies involve peripherally administered cholinergic agents, the association of mesostriatal DA with sensitization would be consistent with a cholinergic striatal mechanism of action.

Thus, increased striatal cholinergic activity appears to inhibit the development of cocaine-induced CPP but heighten context-dependent locomotor sensitization. The former findings are puzzling and somewhat counterintuitive. Striatal ACh is a critical component in the switch from acquisition to consolidation (Rasch *et al*, 2006). It would, therefore, be expected that an increase in striatal ACh would be associated with not only the increased salience of cocaine's effect (as described in a previous section), but also the salience of associated stimuli. The absence of this effect (in fact, the reverse is observed: increased striatal ACh attenuated (Hikida *et al*, 2003) and decreased striatal ACh augmented (Hikida *et al*, 2001) cocaine-induced CPP) may, in part, be due to the NAc target of these studies, as conditioned learning is primarily a function of the dorsal striatum. In particular, the association of TANs with associative learning has been confined to the dorsal striatum (Apicella, 2007). Related findings in the amygdala (below) are also directly relevant.

Conditioned learning and the amygdala. The basolateral portion of the amygdala facilitates the processing of stimuli that are behaviorally relevant when stimulus–outcome associations are being formed (van der Zee and Luiten, 1999). Through this process, environmental cues paired with drug use acquire motivational salience valiance and guide goal-directed responses to these stimuli (See, 2005). Conditioned learning is mediated by basolateral amygdala (BLA) mAChRs, at least in part, as the bilateral infusion of the non-selective mAChR agonist oxotremorine into this region significantly improved retention of an inhibitory avoidance task (Power *et al*, 2003). Also, infusions of the mAChR agonist scopolamine into the BLA impaired the learning of a food CPP task (McIntyre *et al*, 1998). Both M_1 and M_2 ACh receptors appear to be involved, as both telenzipine (a selective M_1 antagonist) and methoctramine (a selective M_2 antagonist) blocked the retention of the avoidance task described above (Power *et al*, 2003).

The amygdala is one of the few brain regions that consistently exhibit increased metabolic activity in response to cocaine-associated cues in both animal (Brown *et al*, 1992; Ciccocioppo *et al*, 2001) and human (Childress *et al*, 1999; Kilts *et al*, 2001) studies, consistent with this region's role in conditioned emotional memories. In preclinical studies, the infusion of scopolamine into the BLA just prior to the acquisition phase of a classical conditioning procedure produced a dose-dependent disruption of cocaine-seeking behavior during cue-induced drug reinstatement (See *et al*, 2003). Drug reinstatement was unaffected when scopolamine was administered in the BLA following successful conditioning and just prior to the expression of conditioned-cue reinstatement (See *et al*, 2003). This is consistent with the disruption of a CPP-related food task with scopolamine described above (Power *et al*, 2003). Interestingly, Zeigler *et al* (1991) have shown a decreased number of amygdalar mACh receptors following the administration of cocaine over 5 days by an implanted pellet (paradigm described earlier). Thus, BLA mAChRs appear to play a role in the acquisition of cocaine-related associations, but not in the expression of previously acquired associations. In contrast, intra-amygdalar injections of the mACh agonist oxotremorine (10 ng/0.5 μl) also facilitated the extinction of amphetamine (2 mg/kg) CPP when administered immediately following the training trial, but not if administered 2 h after the training trial (Schroeder and Packard, 2004). Although both the See *et al* (2003) and Schroeder and Packard (2004) studies reveal that cholinergic interventions suppress the acquisition of stimulant-related associations, the direction of change is different; See *et al* (2003) showed disruption with a cholinergic antagonist, whereas Schroeder and Packard (2004) used a cholinergic agonist. These differences may be a result of the drug association used (cocaine *vs* amphetamine, respectively) and/or the behavior assessed (acquisition *vs* extinction, respectively).

ACETYLCHOLINE AND PREFRONTAL CORTICAL COGNITION

Executive cognitive mechanisms provide the behavioral flexibility to override automatic responses that are no longer adaptive. Examples of executive processes include attentional selection and resistance to interference, behavioral inhibition, set shifting, planning, and decision making. Executive processes primarily occur in the PFC. Acetylcholine has been implicated in several aspects of executive function that appear to be impaired in cocaine addicts, most notable being attentional processes, response inhibition, and set shifting (Adinoff *et al*, in press; Horner *et al*, 1996; Rilling and Adinoff, 2007).

Attentional processes. Attention refers to the different capacities or processes that relate to how an organism becomes receptive to stimuli and how it begins to process incoming or attended-to (internal or external) excitation (Parasuraman, 1998). ACh is strongly linked to these attentional processes (Baxter and Chiba, 1999; Robbins, 2002; Sarter *et al*, 2003). ACh efflux, for example, is increased into the medial frontal cortex during a five-choice serial reaction time task (5-CSRTT)—a measure of visual attention. Rats receiving highly selective ACh immunotoxins (192 IgG-saprin) into the NBM (which projects to the PFC and amygdala) display dose-related decrements in attention parameters on a 5-CSRTT (McGaughy *et al*, 2002). Specifically, the number of ChAT-immunoreactive cells in NBM was significantly correlated with task accuracy (McGaughy *et al*, 2002). The effects of similar basal forebrain lesions (induced by quisqualate) on a visual attention task were reversed following the implantation of ACh-enriched neural grafts into the cortex or following systemic treatment with physostigmine or nicotine, supporting the relevance of ACh to this process (Muir *et al*, 1992, 1995). The rise in NAc DA resulting from exposure to a salient stimulus may focus attention by stimulating cortical ACh efflux (Acquas *et al*, 1994; Day and Fibiger, 1992, 1994; Sarter *et al*, 1999). As noted for striatal and hippocampal increases in ACh, cortical elevations in ACh are blocked by D_1 antagonists (Acquas *et al*, 1994).

Long-term cocaine abuse has been linked to attention and concentration deficits on standardized neurocognitive measures (Ardila *et al*, 1991; Horner *et al*, 1996; Jovanovski *et al*, 2005). In a review of 17 studies, Horner *et al* (1996) tentatively concluded that chronic cocaine use appears to decrease cognitive speed. A more recent review of 15 studies by Jovanovski *et al* (2005) suggested significant deficits in cocaine-addicted subjects on measures that required sustained, focused, and divided attention. In preclinical studies, Dalley *et al* (2005) pre-trained rats in the 5-CSRTT and then exposed them to multiple 'long-access' cycles (five daily sessions repeated on four successive occasions) of cocaine self-administration. Impaired attentional accuracy, increased omissions, and slower latencies were observed 24 h, but not 1 month, following the cessation of cocaine administration. There was, however, no effect on visual attentional performance relative to surgically controlled rats. To our knowledge, there are no empirical studies directly connecting cocaine-induced deficits in attention with ACh.

Set shifting. Set shifting, or response reversal, is a key element of decision making and is required when response contingencies, such as the amount of reward, direction of reward (win or lose), or the time it takes to obtain a reward, are altered. The dorsomedial striatum is one of the regions critical for this behavioral flexibility, and recent experiments suggest that the activation of ACh interneurons within the dorsomedial striatum facilitates behavioral flexibility under conditions of changing contingencies (Ragozzino and Choi, 2004; Ragozzino *et al*, 2002). Activation of muscarinic cholinergic receptors in this region may facilitate the learning of situationally adaptive response patterns. For example, ACh efflux in the dorsal striatum did not change during the acquisition phase of a discrimination task, but increased during the reversal stage as a rat was beginning to learn a new response pattern (Ragozzino and Choi, 2004). Striatal ACh then returned to baseline after a new response pattern was reliably executed. Infusion of the mAChR antagonist scopolamine (8 μg/side, but not 1 μg/side) into the dorsomedial striatum did not impair learning in a simple response discrimination task, but did impair response reversal learning (Ragozzino *et al*, 2002). Chen *et al* (2004) also found that the systemic administration of scopolamine (0.1 and 0.25 mg/kg i.p.) dose-dependently blocked learning of set-shifting paradigms. Although the systemic administration of scopolamine did not allow regional localization of this effect, the absence of an effect by methylscopolamine (which does not cross the blood–brain barrier) demonstrated central mechanisms (Chen *et al*, 2004). Palencia and Ragozzino (2006) also observed an increase in dorsomedial striatal efflux during reversal learning in rats. These investigators suggested that this ACh effect may, at least in part, be mediated by *N*-methyl-D-aspartate (NMDA) glutamate receptors, as dorsomedial NMDA receptor blockade by *dl*-2-amino-5-phosphonopentanoic acid significantly impaired both response reversal learning and concomitant ACh efflux.

The addictive use of cocaine has been linked to poor performance on set-shifting tasks, which require learning new strategies and reject old strategies that are no longer effective (Adinoff *et al* (in press); Rilling and Adinoff, 2007). Impaired performances on such response reversal measures such as the Wisconsin card sorting task (WCST) (Ardila *et al*, 1991; Beatty *et al*, 1995; Rosselli *et al*, 2001) and the trail making test (Trails B) (Beatty *et al*, 1995; Rosselli *et al*, 2001; Smelson *et al*, 1999; Strickland *et al*, 1993) have been demonstrated in cocaine-addicted subjects relative to controls. Although the preclinical literature does not presently provide a link between set-shifting deficits following cocaine administration and alterations in cholinergic systems, recent work from our clinical laboratory suggests such a connection (B Adinoff *et al*, unpublished). In these studies, physostigmine and saline were administered to abstinent cocaine-addicted subjects and healthy controls while at rest. Regional cerebral blood flow (rCBF), a measure of neural activity, was assessed with single photon emission computed tomography (SPECT) following each infusion. On a third study day, set shifting was assessed with both the WCST and intradimensional/extradimensional shift (IED) task (Cambridge, 2002). Scores on each task were then correlated with rCBF following physostigmine (relative to saline) in the orbitofrontal cortex (OFC), a region critical for set-shifting processing. A significant correlation was observed between OFC rCBF following physostigmine and both WCST and IED scores in the healthy controls, but not in the cocaine-addicted subjects. These findings offer preliminary evidence that cholinergic disruption following chronic cocaine use may be associated with deficits in decision making.

SUMMARY AND FUTURE DIRECTIONS FOR CLINICAL RESEARCH

Given the multiple origins and discrete projections of CNS cholinergic neurons and their involvement in a myriad of cognitive functions, the relationship between cocaine and

ACh is predictably complicated. Acutely, cocaine administration increases ACh in the VTA, NAc, and dorsal striatum. Elevations in VTA ACh concentrations following acute cocaine occur via neuronal projections from the mesopontine nuclei and heighten cocaine's rewarding effects, primarily through the M_5 receptor, by complementing DA neuronal input in a feed-forward manner. In contrast, NAc and dorsal striatal increases in ACh are produced via VTA DA afferents upon striatal ACh interneurons. Striatal ACh release (under the modulating influence of D_1 and D_2 receptors) appears to increase cocaine's rewarding effects but decrease cocaine-associated conditioned learning. The chronic administration of cocaine also appears to result in fewer ACh receptors upon abstinence, although the direction of these changes is dependent on cocaine dose, duration, time since last administration, and brain region assessed. nAChRs facilitate the initiation of VTA cocaine-induced sensitization, whereas NAc mAChRs inhibit NAc sensitization.

Cocaine reinforces different types of learning by initiating the storage of new information and strengthening neural pathways through the process of synaptic plasticity. Since cocaine also increases extracellular levels of ACh and ACh turnover rates within the hippocampus, high levels of hippocampal ACh during cocaine use may facilitate the encoding of explicit drug-related information. The acquisition of cocaine-related associations thought to underlie craving is altered by cholinergic release in both the amygdala and striatum, although the direction of change effected is uncertain. Although ACh likely plays a role in the cocaine-related deficits observed in executive functioning, this relationship has yet to be demonstrated and remains a critical area of investigation.

In summary, a plethora of studies now clearly document that the cholinergic system is involved to a great extent in both the experience of cocaine and the conditioned association of cocaine with salient stimuli. This association is complicated by the multiple origins of cholinergic neurons, the unique aspects of striatal cholinergic neurons, and the presence of inhibitory and excitatory ACh subtypes. Our review was also focused on mACh receptor systems with only limited attention on the nACh receptors. Internal and external feedback systems, specific for each cholinergic system, further complicate interpretation. Thus, clarification of the role of ACh in cocaine addiction requires increasing use of agonists and antagonists specific for receptor subtype, as well as animals bred with specific subtype deficits.

The above-reviewed studies do not involve humans, with the exception of a few. These preclinical studies, however, strongly support a role of ACh receptor systems in the progression of cocaine from initial reward to the maintenance of addictive-like behaviors. Complementary clinical laboratory studies to examine the link between chronic cocaine use and ACh receptor alterations, as well as pharmacological trials to assess the utility of cholinomimetics in the treatment of cocaine dependence, are now required. Initially, neuroimaging studies can be used to investigate alterations in ACh receptor systems in cocaine-addicted subjects. SPECT, PET, and functional magnetic resonance imaging (fMRI) techniques have been used to great advantage in the investigation of cholinergic functioning in other populations, particularly in Alzheimer's disease (Volkow *et al*, 2001). For example, PET and SPECT ligands are available to assess extracellular ACh, ACh receptors, and brain function (ie brain blood flow and glucose utilization) as well as markers of cholinergic cell viability (vesicular transporters, AChE) (Zubieta *et al*, 1998). Radioligands can be used to identify mAChRs (Volkow *et al*, 2001) and nAChRs (Ma *et al*, 2002), and more recently developed tracers can select for M_2 receptor subtypes (Furey *et al*, 2000). These techniques may also be used to explore cocaine-related deficits in executive function, such as learning tasks relevant to the addictive process, in the presence or absence of cholinergic agonist or antagonists. For example, Furey *et al* (2000) have utilized fMRI to explore cognitive-induced alterations in neural activation during a working memory task concurrent with the infusion of physostigmine. Given the importance of ACh in modulating the tonic and clonic release of DA, the concurrent functional assessment of DA and ACh systems during acute cocaine administration, withdrawal, and extended abstinence in addicted patients may elucidate the convergent interaction and relevant disruptions in these two complementary systems.

In the first, and as yet preliminary, study to utilize neuroimaging techniques to assess ACh systems in cocaine-addicted subjects, we have used SPECT to identify alterations in ACh systems in abstinent cocaine-addicted subjects. Preliminary findings suggest regional-specific changes in cerebral blood flow following the infusion of physostigmine or scopolamine compared to saline (Adinoff *et al*, 2005). To date, the only published studies exploring neural cholinergic systems in this population have reported that ChAT and vesicular ACh transporter (VAChT) concentrations in the autopsied brains of cocaine-addicted subjects did not differ from those of heroin-addicted (VAChT, ChAT) or control subjects (VAChT) (Kish *et al*, 1999; Siegal *et al*, 2004).

Ultimately, pharmacologic investigations will be required to explore the relevance of ACh alterations to the addictive process. Although cocaine increases ACh during acute administration, the literature reviewed above, *in toto*, suggests that ACh agonists may be the most promising agents in the treatment of cocaine dependence. Cholinomimetics may compensate for the apparent reduction in ACh receptors observed during withdrawal and facilitate the acquisition of non-cocaine-driven behaviors by strengthening the salience of stimuli unassociated with cocaine use. A large number of cholinergic agonists are now available for human use, and pharmaceutical agents that target specific receptor subtypes are rapidly being developed. Some of the most common cholinergic agonists are cholinesterase inhibitors, and donepezil, galantamine, and rivastigmine are presently available for use in humans (Cummings, 2000; Ellis, 2005). In a preliminary trial of donepezil using the Cocaine Rapid Efficacy and Safety Trial (CREST) study design, however, dozepezil did not produce significant changes in cocaine use (Winhusen *et al*, 2005). Treatment trials of rivastigmine in the treatment of cocaine addiction are ongoing. The relevance of the M_5 receptor in cocaine reinforcement (Fink-Jensen *et al*, 2003; Thomsen *et al*, 2005) suggests that targeting this muscarinic subtype may be of particular importance.

In contrast, a clinical laboratory study revealed that the nicotinic receptor *antagonist* mecamylamine decreased craving in cocaine-dependent subjects (Reid *et al*, 1999), although its effectiveness in relapse prevention is unknown. This mirrors preclinical work demonstrating that mecamylamine suppressed both nicotine and cocaine self-administration (Blokhina *et al*, 2005). These studies highlight the difficulty of dissembling the contributions of cocaine *vs* nicotine to nAChR changes in cocaine- (and typically nicotine-) addicted individuals. In preclinical studies, the administration of nicotine alters the locomotor effects of cocaine (Collins and Izenwasser, 2004), the two drugs exhibit cross-tolerance (Desai and Terry, 2003), nicotine substitutes for cocaine reinforcement (Tessari *et al*, 1995), and repeated nicotine exposure enhances cocaine-seeking behavior (Bechtholt and Mark, 2002). In humans, nicotine increases cue-induced cocaine craving (Reid *et al*, 1998). Thus, the frequent co-morbid dependence on nicotine and cocaine, their shared effects on reward systems (Kauer, 2003), and their apparent interactive effects on the ACh system suggest that the nAChR may be a fruitful area of investigation. The newly available (for nicotine dependence) partial $\alpha_4\beta_2$ nicotinic agonist, varenicline, may therefore be worthy of investigation for the treatment of cocaine dependence.

Perhaps one of the most promising treatment strategies involves the shared role of both DA and ACh in regulating reward and each other's synaptic release. From a clinical perspective, this neurobiologic interconnectiveness suggests that a combination of cholinergic and dopaminergic modulation may be the optimal treatment approach for the cocaine-dependent patient. For example, most studies of DA agonists have not provided strong signals in the treatment of cocaine dependence (Adinoff, 2004). The addition of a cholinomimetic may enhance the effects of a dopaminergic agonist in the NAc. Alternatively, a pharmacologic cocktail of DA agonist and cholinergic antagonist may provide the optimal environment during the early phase of cocaine abstinence. Clearly, other neurotransmitter systems that regulate ACh outflow and pharmacogenetic influences are also potent areas of investigation.

Ultimately, one of the greatest benefits derived from ACh modulation in the treatment of cocaine addiction may stem from its effects on learning and memory processes. These changes may account for some of the more intractable aspects of cocaine addiction, such as craving, sensitization, and conditioned learning. A better delineation of the molecular and cellular changes that occur during chronic cocaine use may provide important insights into the role of ACh in cocaine addiction, assisting in the development of stage- and site-specific pharmacological treatment interventions.

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