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Perspective

There and Back Again: A Tale of Norepinephrine and Drug Addiction

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Fueled by anatomical, electrophysiological, and pharmacological analyses of endogenous brain reward systems, norepinephrine (NE) was identified as a key mediator of both natural and drug-induced reward in the late 1960s and early 1970s. However, reward experiments from the mid-1970s that could distinguish between the noradrenergic and dopaminergic systems resulted in the prevailing view that dopamine (DA) was the primary 'reward transmitter' (a belief holding some sway still today), thereby pushing NE into the background. Most damaging to the NE hypothesis of reward were studies demonstrating that NE receptor antagonists and NE reuptake inhibitors failed to impact drug self-administration. In recent years new tools, such as genetically engineered mice, and new experimental paradigms, such as reinstatement of drug seeking following withdrawal, have propelled NE back into the awareness of addiction researchers. Of particular interest is disulfiram, an inhibitor of the NE biosynthetic enzyme dopamine β-hydroxylase, which has demonstrated promising efficacy in the treatment of cocaine dependence in preliminary clinical trials. The purpose of this review is to synthesize the new data linking NE to critical aspects of DA signaling and drug addiction, with a focus on psychostimulants (eg, cocaine), opiates (eg, morphine), and alcohol.

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INTRODUCTION

Norepinephrine (NE) is one of the most abundant neurotransmitters in the brain, where it plays an important role in selective attention, general arousal, and stress reactions in challenging environments (Foote *et al*, 1983; Levine *et al*, 1990; Berridge and Waterhouse, 2003; Aston-Jones and Cohen, 2005). NE has also been implicated in diverse central processes and diseases, including learning and memory, neuronal excitability, pain, and affective disorders (Ressler and Nemeroff, 1999; Gibbs and Summers, 2002; Jasmin *et al*, 2002; Weinshenker *et al*, 2001; Murchison *et al*, 2004).

The brain noradrenergic system is comprised of two main ascending projections: the dorsal noradrenergic bundle (DNB), which originates in the A6 locus coeruleus (LC) and projects to the hippocampus, cerebellum, and forebrain, and the ventral noradrenergic bundle (VNB), which arises in a number of nuclei of the pons and medulla, such as the A1 and A2 cell groups, and innervates the hypothalamus, midbrain, and extended amygdala (reviewed by Moore and Bloom, 1979). These neuroanatomical substrates underlie NE's ability to impinge upon brain systems that control multiple aspects of drug addiction, including sensitization, reward, and relapse.

This review is comprised of four main parts. In the first, we will summarize the early studies that identified NE as an important mediator of drug reward, as well as the subsequent experiments implicating dopamine (DA) that led to the downfall of the noradrenergic theory of reward. Second, we will review the recent literature placing NE at the forefront again as a critical mediator of drug reward and the addiction process, with a focus on psychostimulants, opiates, and ethanol. Third, we will catalog the interplay between the noradrenergic and dopaminergic systems underlying at least some of the effects of NE on drug reward. Finally, we will review clinical studies assessing the effects of noradrenergic gene polymorphisms on drug responses and the efficacy of compounds that modulate NE signaling for the treatment of drug addiction.

PART I: THE RISE AND FALL OF THE NORADRENERGIC THEORY OF DRUG REWARD

NE was implicated as a key mediator of drug reward for three primary reasons: noradrenergic pathways support intracranial self-stimulation (ICSS) and modulate

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drug-induced changes in ICSS threshold; the biochemical activity of psychostimulant drugs includes blockade of NE reuptake and enhancement of NE release; and compounds that interfere with NE synthesis or signaling influence drug self-administration (SA).

NE and Intracranial Self-Stimulation

ICSS, which refers to the ability of animals to operantly administer electrical stimulation to the brain, was first described by Olds and Milner (1954). The fact that electrodes placed in some regions of the brain (but not others) could support ICSS implied that anatomically specialized reward systems existed in the brain, and many subsequent studies were designed to dissect the neurochemical basis of these reward pathways (Wise, 1978). NE was first hypothesized as a key reward neurotransmitter in the early 1960s (Poschel and Ninteman, 1963; Stein, 1964)—a hypothesis that was supported when self-stimulation sites were found in the LC and along the DNB projection path (Dresse, 1966; Crow *et al*, 1972; Ritter and Stein, 1973). Positive self-stimulation sites were also found along the VNB (Ritter and Stein, 1974). Furthermore, NE is released during medial forebrain bundle (MFB) ICSS, and central administration of NE facilitates MFB ICSS (Stein and Wise, 1969; Wise and Stein, 1969; Wise *et al*, 1973). Finally, drugs that deplete NE stores, interfere with NE synthesis, or ablate NE neurons disrupt ICSS (reviewed by Fibiger and Phillips, 1974; Wise, 1978).

The idea that drugs of abuse act via the endogenous reward systems in the brain first arose when psychostimulants (eg, amphetamine, cocaine) were found to alter ICSS thresholds (Stein, 1964; Crow, 1970; Wise, 1978). One interpretation of these results was that NE mediates the effect of psychostimulants on ICSS, because these drugs cause NE release, block NE reuptake, or both.

Yet despite evidence supporting the role of NE in ICSS, a number of subsequent studies cast doubt on its importance. Some groups were unable to reproduce the original finding that the LC could support self-stimulation (Amaral and Routtenberg, 1975; Simon *et al*, 1975). Furthermore, 6-hydroxydopmaine (6-OHDA) or electrolytic lesions of the DNB failed to attenuate LC self-stimulation, and LC lesions failed to disrupt self-stimulation of sites along the DNB. ICSS was also unaffected by administration of antagonists at low doses that are selective for adrenergic receptors (reviewed by Wise, 1978). Taken together, these findings suggest that, whereas NE might contribute to ICSS and reward, it is by no means a critical component of this system.

Contemporaneously with the above studies, a number of groups were investigating the possibility that DA, not NE, was the critical neurotransmitter mediator of ICSS and endogenous reward. These studies have been extensively reviewed elsewhere (eg, Wise, 1978), but to summarize, DA passed many of the criteria that NE failed. For example, self-stimulation sites were also found at DA cell bodies and projection fields, and nearly all the pharmacological agents used to implicate NE (eg, reserpine, 6-OHDA, amphetamine, cocaine, and α-methyl-p-tyrosine (AMPT)) also affect dopaminergic systems. Most importantly, selective destruction of DA neurons or blockade of DA receptors profoundly attenuate ICSS. By the late 1970s DA, rather than NE, was generally accepted as the brain's primary 'reward neurotransmitter' in the context of ICSS.

NE and Psychostimulant SA

Rodents and nonhuman primates will perform operant tasks (eg, lever press, nose poke) for intravenous and intracranial injections of drugs that are abused by humans, including psychostimulants (eg, cocaine, amphetamine), and opiates (eg, morphine, heroin). Experiments using alcohol typically involve operant or voluntary oral ethanol ingestion. Collectively, these 'SA paradigms are generally considered the gold standard for assessing the reinforcing properties of a drug. There are four distinct phases of SA: acquisition (when the animal learns the operant behavior), maintenance (when drug intake patterns are stable), extinction (when the operant behavior is extinguished by substitution of an inactive solution for the drug), and reinstatement (when the operant behavior is restored by contextual cues, stress, or drug priming). Until recently, the maintenance phase was usually the only one used to assess and interpret addiction pathways, and this phase is often synonymous with SA itself.

Relatively early on, catecholamines were found to be critical for psychostimulant SA, as catecholamine synthesis inhibitors or nonselective catecholamine receptor antagonists produced effects similar to reward reduction and termination (reviewed by Wise, 1978). When treatments that could distinguish between the contributions of noradrenergic and dopaminergic systems were tested, it became clear that DA, not NE, was the primary mediator of psychostimulant SA. For example, DA receptor antagonists increase the response rate for amphetamine or cocaine, whereas NE receptor antagonists have little or no effect (Yokel and Wise, 1975, 1976; Woolverton, 1987). Two studies (Goldberg and Gonzalez, 1976; Harris *et al*, 1996) demonstrated a decrease in cocaine SA following treatment with propanolol, a β-antagonist, but there was a concomitant decrease in responding for food in the latter study, suggesting a nonspecific effect on task performance. Although 6-OHDA lesions of DA produce a long-lasting reduction in SA of cocaine, lesions of both the dorsal and VNBs fail to alter responding (Roberts *et al*, 1977). Furthermore, while selective DA reuptake inhibitors themselves are readily self-administered and alter psychostimulant SA, selective NET inhibitors possess neither property (Woolverton, 1987; Howell and Byrd, 1991; Skjoldager *et al*, 1993; Tella, 1995; Wee *et al*, 2006). The only noradrenergic drug that appears to have reinforcing properties is clonidine, an α2-adrenergic receptor (α2AR) agonist that is self-administered by both rats and nonhuman primates (Shearman *et al*, 1981; Woolverton *et al*, 1982). The α2ARs are located on noradrenergic neurons, where they function as inhibitory autoreceptors, as well as on the dendrites and terminals of NE target cells—the latter population of α2ARs appears to mediate the rewarding effects of clonidine (Cervo *et al*, 1993). The mechanism by which clonidine produces its reinforcing effects is not clear. However, it is interesting to note that α2ARs, especially the α2cAR subtype, are highly expressed in striatum and can be activated by DA. Given the relatively sparse innervation of the striatum by noradrenergic neurons (especially the dorsal striatum), the suggestion is that DA is the primary endogenous ligand for α2ARs in the striatum (Zhang *et al*,

1999). Perhaps the rewarding effects of clonidine are mediated by direct activation of striatal α2ARs, which likely converge on some of the striatal signaling pathways activated by DA—a hypothesis that could be tested directly by assessing SA of clonidine directly into the striatum.

As a whole, these studies solidified the DA hypothesis of drug reward whereas refuting an important role for NE, and NE naturally faded from the consciousness of most psychostimulant addiction researchers until the late 1990s. However, there are some crucial points that must be emphasized here. First, all the SA studies we have mentioned examined one phase of SA only: maintenance of an established behavior. The influences of NE on acquisition, extinction, and reinstatement of drug-seeking behavior, which model other critical aspects of drug addiction, were not tested. There are more recent studies (to be discussed later) that have strongly implicated NE as a critical mediator of reinstatement of an extinguished SA. The second point is that SA is only one way of measuring drug reward. As will be seen in subsequent sections of this review, the conclusions drawn are much different when one considers investigations using conditioned place preference (CPP).

NE and Opiate SA

As with psychostimulant SA, research in the 1970s began to emphasize the importance of catecholamines in the mediation of opiate SA. A series of experiments demonstrated that depletion of NE and DA with AMPT, (which inhibits tyrosine hydroxylase) prevents or attenuates the SA of morphine in rodents (Davis and Smith, 1977) and in nonhuman primates (Pozuelo and Kerr, 1972). When treatments that could distinguish between the contributions of NE and DA were developed, researchers began to elucidate a role for NE in the mediation of morphine's behavioral effects. For example, reduction of NE synthesis with FLA-57, a dopamine β-hydroxylase (DBH) inhibitor, attenuates the oral intake of morphine in rats (Brown *et al*, 1978). Nonetheless, despite this demonstration, most research in the 1970s and 1980s focused on DA mediation of morphine reinforcement at the expense of NE, due in large part to the emerging DA hypothesis of psychostimulant SA.

Research into the DA hypothesis of opiate reinforcement has indeed indicated a role for this neurotransmitter, but experimental results have been fraught with inconsistencies (reviewed by Pierce and Kumaresan, 2006). For example, while 6-OHDA lesions do impair the acquisition of heroin SA (Singer and Wallace, 1984) and decrease morphine SA (Smith *et al*, 1985) in some studies, these results are not always replicated (Pettit *et al*, 1984; Dworkin *et al*, 1988, Gerrits and Van Ree, 1996). In addition, DA receptor antagonism does not consistently alter opiate SA behavior (Ettenberg *et al*, 1982; Van Ree and Ramsey, 1987; Gerber and Wise, 1989; Gerrits *et al*, 1994).

NE and Ethanol SA

Following the pattern established by psychostimulants and opiates, DA has been the main focus of research examining the neurochemical mediation of ethanol's reinforcing effects (Wise, 1980; Koob *et al*, 1998). Electrophysiological, pharmacological, and genetic experiments have established a clear role for DA in voluntary ethanol consumption (eg, Koob *et al*, 1994; El-Ghundi *et al*, 1998; Phillips *et al*, 1998). For example, SA of ethanol increases nucleus accumbens (Nac) DA release in rodents (Weiss *et al*, 1993, 1996; Gonzales and Weiss, 1998; Nurmi *et al*, 1998; Olive *et al*, 2000; Melendez *et al*, 2002; Hungund *et al*, 2003), and DA D1 and D2 receptor agonists and antagonists modulate ethanol SA in some circumstances (Weiss *et al*, 1990; Hubbell *et al*, 1991; Dyr *et al*, 1993; Rassnick *et al*, 1993a; Ng and George, 1994; Silvestre *et al*, 1996; Cohen *et al*, 1998, 1999; Boyce and Risinger, 2002; D'Souza *et al*, 2003; Zocchi *et al*, 2003). In addition, genetic deletion of D1 or D2 DA receptors decreases ethanol SA (El-Ghundi *et al*, 1998; Phillips *et al*, 1998; Risinger *et al*, 2000). However, inconsistencies similar to those obtained in examining the DA mediation of opiate reinforcement have plagued the field. For example, 6-OHDA lesions of the NAc do not alter ethanol SA in rats (Lyness and Smith, 1992; Rassnick *et al*, 1993b; Ikemoto *et al*, 1997, Koistinen *et al*, 2001). Further, there have been some conflicting results regarding the effects of pretreatment with dopaminergic agents (Goodwin *et al*, 1996; Silvestre *et al*, 1996).

For these reasons, alternate hypotheses of the neurochemistry of ethanol reinforcement have been postulated, including the suggestion that NE, and not DA, is the critical neurotransmitter (Amit and Brown, 1982). For example, acute administration of ethanol modulates the synthesis, turnover, and release of central NE (Corrodi *et al*, 1966; Carlsson and Lindqvist, 1973; Hunt and Majchrowicz, 1974; Pohorecky and Jaffe, 1975; Karoum *et al*, 1976), and the activity of noradrenergic neurons (Aston-Jones *et al*, 1982; Pohorecky and Brick, 1988; Verbanck *et al*, 1990). Moreover, ethanol has a greater effect on NE turnover and release than on DA (Corrodi *et al*, 1966; Hunt and Majchrowicz, 1974). Both chemical lesioning of the NE system and blocking NE synthesis via DBH inhibitors reduce voluntary ethanol intake, whereas DA lesions do not (Brown *et al*, 1977; Kiianmaa *et al*, 1979; Rassnick *et al*, 1993b).

Although these studies indicate an important role for NE in ethanol-mediated behaviors, other conflicting research has muddied the waters. Depending on the site of administration and the strain of rat used, chemical lesions of noradrenergic neurons with 6-OHDA can increase (Melchior and Myers, 1976; Kiianmaa, 1980), decrease (Melchior and Myers, 1976; Corcoran, Lewis, and Fibiger, 1983), or have no effect (Melchior and Myers, 1976; Richardson and Novakovski, 1978) on voluntary ethanol consumption. There are also conflicting data on DBH inhibitors (Amit *et al*, 1977; Daoust *et al*, 1990) and adrenergic agonists (Andreas *et al*, 1983; Grupp *et al*, 1989). Yet in spite of these conflicting results, most research has favored a prominent role for noradrenergic function in alcohol reward.

PART II: THE NORADRENERGIC THEORY OF DRUG REWARD: A RESURRECTION

NE and Psychostimulant-Induced Locomotion/ Sensitization

Although not strictly a test of potential drug reward, measurement of locomotor activity has been critical to

understanding molecules and pathways contributing to drug addiction for two key reasons. First, most drugs of abuse—including psychostimulants, opiates, and ethanol—produce locomotor hyperactivity, making this trait a generally reliable (albeit imperfect) predictor of abuse potential. Drug-induced locomotor hyperactivity is profoundly robust and reproducible, and the study of brain regions and signaling pathways controlling this phenomenon has significantly contributed to our understanding of how addictive drugs affect the brain. Second, drug-induced locomotor activity demonstrates sensitization, which may model progressive drug craving during the addiction process and manifests as increasing hyperactivity in response to the repeated administration of drugs of abuse (reviewed by Robinson and Berridge, 2000).

In sharp contrast to the paucity of SA data supporting the role of NE in psychostimulant addiction, another collection of studies has established that NE—acting primarily via α1-adrenergic receptors (α1ARs)—is essential for drug-induced locomotor activity and sensitization. For example, LC lesions attenuate amphetamine-induced locomotion (Mohammed *et al*, 1986). Also, administration of the α1AR antagonist prazosin, either systemically or directly into the prefrontal cortex (PFC), reduces both amphetamine- and cocaine-induced locomotion and sensitization (Snoddy and Tessel, 1985; Dickenson *et al*, 1988; Blanc *et al*, 1994; Darracq *et al*, 1998; Drouin *et al*, 2002; Weinshenker *et al*, 2002a; Wellman *et al*, 2002; Auclair *et al*, 2004; Salomon *et al*, 2006). Furthermore, α1bAR knockout mice are refractory to psychostimulant-induced locomotor activity and sensitization (Drouin *et al*, 2002; Auclair *et al*, 2004; Salomon *et al*, 2006). Conversely, elevating extracellular NE levels via blockade of α2AR inhibitory autoreceptors or via genetic ablation of the NE transporter (NET) increases the locomotor response to psychostimulants (Xu *et al*, 2000; Villégier *et al*, 2003). Although not as exhaustively investigated, α2- and βARs also appear to modulate this drug-induced behavior (Harris *et al*, 1996; Villégier *et al*, 2003). When combined, the results of these studies provide compelling evidence that NE is critical for psychostimulant-induced locomotor activity and sensitization.

NE and Psychostimulant CPP

CPP has recently been among the most popular measures of drug reward. In this paradigm, one set of contextual cues is paired with the drug of interest, whereas a different set of cues is paired with a vehicle control. After initial conditioning, an animal is then allowed unrestricted access to both contexts in the absence of drug, and an increase in time spent in the drug-paired context is interpreted as drug-associated reward. Although most drugs that support operant SA also support a CPP in rodents, there are some discrepancies, and each paradigm likely measures distinct reward processes. The primary differences involve active (SA) *vs* passive (CPP) drug administration, and operant responding for 'immediate' reward (SA) *vs* expression of a learned context-drug reward association in a drug-free state (CPP). Both paradigms have inherent advantages and disadvantages, and both have helped reveal molecules and circuits underlying drug reward (reviewed by Bardo and Bevins, 2000).

Surprisingly, there are few studies investigating the possible role of NE in psychostimulant CPP. Ventura *et al* (2003) found that a selective depletion of NE in the PFC abolishes amphetamine CPP in mice, whereas NET knockout mice with excess levels of extracellular NE show enhanced cocaine CPP. One caveat before drawing conclusions based on these results: NE is known to play an important role in some aspects of learning and memory. Because CPP is an associative learning paradigm, manipulations of NE could alter the development or expression of a psychostimulant CPP in the absence of any effect on the rewarding properties of the drugs. However, this is unlikely, as mice that completely lack NE still express a normal conditioned taste aversion to lithium chloride and ethanol and show a CPP to food (Weinshenker *et al*, 2000; Schank *et al*, 2006; Olson *et al*, 2006). Interestingly, NE depletion early in development either has no effect (neonatal 6-OHDA lesion; Spyraki *et al*, 1982a) or even enhances (DBH knockout mice; Schank *et al*, 2006) psychostimulant CPP, probably due to compensatory changes in the DA system during development (see below). NE may be an important mediator of the aspects of drug reward that are measured by the CPP paradigm, but clearly more work is required to define its influence, particularly with regard to the effects of adrenergic agonists and antagonists. This is an especially intriguing question—whereas DA is necessary for amphetamine CPP, it may not be necessary for cocaine CPP under all conditions (Spyraki *et al*, 1982a, b; Miner *et al*, 1995; Baker *et al*, 1996; Sora *et al*, 1998; Tzschentke and Schmidt, 1998).

NE and Psychostimulant SA: A Reassessment

Owing to the absence of noradrenergic drug effects on SA (with the exception of clonidine), NE was simply written off as a potential mediator of psychostimulant reinforcement. Again, however, this conclusion was based on data examining a single phase of SA: the maintenance of a previously learned behavior. Primary reinforcement is only one facet of drug addiction, and perhaps not even the most important one, at least from a clinical standpoint. Current concepts in pharmacotherapy for drug dependence have aimed at preventing relapse, rather than disrupting primary reinforcement. The reinstatement phase of SA, during which noncontingent drug priming, drug-associated cues, or stress can trigger a previously extinct SA behavior, has become the standard paradigm for studying relapse (reviewed by Shaham *et al*, 2003).

In stark contrast to the lack of influence on maintenance of psychostimulant SA, the effects of noradrenergic drugs on reinstatement of cocaine and amphetamine drug seeking are profound and clear. NE was first implicated in reinstatement by Davis *et al* (1975). They found that DBH inhibitors that block NE synthesis attenuate reinstatement of amphetamine SA. The clearest case for noradrenergic involvement emerges in the stress-induced reinstatement paradigm. Systemic administration of clonidine or guanabenz, α2AR agonists that decrease NE release by activating inhibitory autoreceptors, attenuates footshock-induced reinstatement in rats (Erb *et al*, 2000). Furthermore, blockade of α2AR autoreceptors with either yohimbine or RS-79948 reinstates cocaine seeking in squirrel monkeys in the

absence of any stressors (Lee *et al*, 2004). These effects likely involve stress-related circuitry in the extended amygdala, as local infusions of βAR antagonists in the bed nucleus of the stria terminalis (BNST) or in the central nucleus of the amygdala (CeA) also block footshock-induced reinstatement of cocaine SA in rats (Leri *et al*, 2002). Intriguingly, chronic cocaine SA in rhesus monkeys elevates NET density in the BNST to a greater extent than any reported changes in DAT, D1, or D2 receptors within the striatum of the same monkeys (Letchworth *et al*, 2001; Nader *et al*, 2002; Porrino *et al*, 2002; Macey *et al*, 2003). Given the known role of NE in central stress responses, these results indicate that NE release in the extended amygdala is required for stress-induced reinstatement. Again, while not necessarily pivotal for primary drug reinforcement, NE is certainly involved in another crucial aspect of addiction. Also of note here is the fact that the influence of NE on reinstatement is not limited to stress paradigms. Noncontigent injections of cocaine powerfully reinstate cocaine SA in normal rats, but not those pretreated with the α1AR antagonist prazosin (Zhang and Kosten, 2005). Because the βAR antagonists do not block cocaine-induced reinstatement, this would suggest that NE is critical for both stress- and drug-primed reinstatement, but via distinct receptors and pathways.

Finally, there are a few recent studies that have used new tools to reassess the role of the noradrenergic system in primary psychostimulant reinforcement. In a SA paradigm, NET knockout mice that have excess extracellular NE show a four-fold increase in their rate of cocaine intake, suggesting that chronic NET ablation causes a decrease in the reinforcing properties of cocaine (Rocha *et al*, 2003). Furthermore, while wild-type mice readily self-administer cocaine orally in a two-bottle free-choice paradigm, α1bAR knockout mice do not (Drouin *et al*, 2002). This is probably due to differences in drug reward sensation, not taste perception, as no genotype differences were observed for sucrose preference or quinine aversion. These results indicate that genetic alterations in noradrenergic pathways can modify the reinforcing properties of cocaine.

NE and Opiate-Induced Locomotion/Sensitization

As with the studies on the SA of psychostimulants, opiates, and ethanol, early experiments on morphine-induced locomotion highlighted the role of catecholamines in mediation of opiate-induced changes in locomotor activity. Inhibition of NE and DA synthesis with AMPT attenuates morphine-induced locomotion (Eidelberg and Schwartz, 1970; Davis *et al*, 1972; Buxbaum *et al*, 1973; Ayhan and Randrup, 1973). Subsequent research into the neurochemistry of morphine-induced locomotion revealed an important role for NE. Specific NE depletion by 6-OHDA lesions of the DNB potentiates the locomotor depressant and cataleptic effects of morphine in rats (Roberts *et al*, 1978). Moreover, pretreatment with FLA-63, a DBH inhibitor, reduces morphine-induced locomotion in rats (Ayhan and Randrup, 1973). In addition, the α-adrenergic antagonist, phenoxybenzamine, decreases the locomotion induced by morphine in mice (Estler, 1973) and rats (Ayhan and Randrup, 1973). Recent research has identified noradrenergic receptors within the PFC as being particularly important in subserving the locomotor effects of morphine. Infusions of prazosin, an α1-adrenergic antagonist, into this brain region attenuate the acute locomotor responses produced by morphine (Drouin *et al*, 2001).

Additional evidence for NE mediation of opiate-induced locomotion comes from genetic alterations of NE function. For example, morphine-induced locomotion is abolished in DBH knockout mice that lack NE, a deficit that is partially reversed by pharmacological restoration of NE or viral-mediated reexpression of DBH in the DNB or VNB (Olson *et al*, 2006). In addition, both genetic deletion and pharmacological blockade of α1bARs prevent morphine-induced locomotion (Drouin *et al*, 2002) and the development of locomotor sensitization (Auclair *et al*, 2004). Overall, the preponderance of available evidence indicates that NE is critical for the locomotor-activating effects of opiates.

NE and Opiate CPP

Similar to the pattern that emerged with studies examining the neurochemical substrates of behavioral actions associated with commonly abused drugs, early research on the neurochemistry of opiate CPP first examined the role of catecholamines as a group, then quickly came to focus on DA almost exclusively, once examination of NE function led to negative results. For example, in one of the earliest adaptations of the CPP paradigm (adapted from Beach, 1957), Schwartz and Marchok (1974) found that morphine approach responses to a Y-maze arm are attenuated by administration of the catecholamine inhibitor, AMPT. Further examination with haloperidol (a DA antagonist) and DETC (a DBH inhibitor) revealed that DA receptor blockade, but not NE inhibition, prevents morphine CPP. Similarly, both 6-OHDA lesions and haloperidol—but not neonatal 6-OHDA injections in rat pups (which leads to whole-brain depletion of NE)—attenuate heroin CPP (Spyraki *et al*, 1983). However, as mentioned previously, possible compensatory changes in the DA system during development could explain the lack of effect from the neonatal 6-OHDA injections. In fact, more recent work has indicated that DA is not required for opiate CPP. For example, mice utterly devoid of DA have surprisingly normal morphine CPP development, and simultaneous blockade of D1 and D2 receptors has no effect on the morphine CPP of drug-naïve animals (Laviolette *et al*, 2002; Hnasko *et al*, 2005). Together, these results suggest the existence of both DA-dependent and DA-independent pathways for opiate CPP.

Could the noradrenergic system be a part of the DA-independent pathway? Despite the relatively inauspicious debut of NE manipulations on opioid CPP, recent research indicates the necessity of noradrenergic function in the establishment of morphine CPP. For example, clonidine, an α2AR agonist, disrupts the establishment of a heroin CPP in rats, presumably by inhibiting NE release (Hand *et al*, 1989). In addition, both clonidine and prazosin (an α1AR antagonist) attenuate morphine CPP in mice, whereas yohimbine (another α2AR antagonist) increases morphine CPP (Zarrindast *et al*, 2002; Sahraei *et al*, 2004). Further-

more, both DBH knockout mice, which are incapable of producing NE, and α1bAR knockout mice fail to express a CPP over a wide range of morphine doses (Drouin *et al*, 2002; Olson *et al*, 2006). It is important to note in this context that morphine CPP can be restored in *Dbh* −/− mice by viral-mediated expression of *DBH* in the VNB (Olson *et al*, 2006). Finally, selective depletion of medial PFC noradrenergic afferents abolishes morphine CPP in mice (Ventura *et al*, 2005). Therefore, the present-day picture that is emerging indicates that NE is indeed required for the establishment of opiate CPP.

NE and Opiate SA: A Reassessment

A combination of several key factors suggests the need for a reexamination of NE's role in morphine SA: the inadequacies of the DA hypothesis of morphine reinforcement; the reduction of voluntary morphine intake following NE inhibition; and the importance of NE for morphine-induced locomotion and CPP. Moreover, the use of new tools (eg, subtype-specific noradrenergic agonists and antagonists, genetic manipulations) would provide a more accurate representation of NE's role in the mediation of opiate abuse. One study used knockout mice to reassess the role of the noradrenergic system in primary opiate reinforcement. Although wild-type mice readily self-administer morphine orally in a two-bottle free-choice paradigm, α1bAR knockout mice do not (Drouin *et al*, 2002). This result is probably due to differences in drug reward, rather than taste perception, as no genotype differences were observed for sucrose preference or quinine aversion.

As opposed to the relative dearth of information on NE mediation of morphine SA, the role of NE on reinstatement of opiate drug seeking—measured by either the reinstatement of drug SA or CPP—is emerging. NE was first implicated in reinstatement by Davis *et al* (1975), who found that DBH inhibitors attenuate the spontaneous reestablishment of opiate SA following a period of extinction. In addition, selective depletion of medial PFC noradrenergic afferents abolishes the reinstatement of an extinguished morphine CPP that has been produced by a priming injection of morphine (Ventura *et al*, 2005). Moreover, chronic treatment with venlaxfaxine, a dual NE/5-HT reuptake inhibitor, attenuates the reacquisition of a morphine CPP by a priming injection of morphine, whereas chronic treatment with the DA D2 antagonist, sulpiride, does not (Lu *et al*, 2001). These data indicate that morphine-seeking behavior induced by morphine abstinence or priming injections is at least partially mediated by NE.

In addition to relapse induced by morphine itself, stress-induced reinstatement of morphine SA also appears to be modulated by NE, as noted with psychostimulants. For example, both 6-OHDA lesions of the VNB and infusion of the α2AR agonist, clonidine, into the BNST block stress-induced reinstatement of morphine CPP (Wang *et al*, 2001). In addition, clonidine also prevents the stress-induced reinstatement of heroin-seeking behavior in rats (Shaham *et al*, 2000). Thus, NE appears to be critical for the stress-induced reinstatement of multiple classes of addictive drugs—a trend that extends even to ethanol, as we will see below.

NE and Opiate Withdrawal

The involvement of NE in opiate withdrawal has been exhaustively documented, and the reader is referred to several recent reviews (Nestler *et al*, 1994, 1999; Maldonado, 1997; Van Bockstaele *et al*, 2001). To avoid unnecessary redundancy, coverage of the subject will be omitted here.

NE and Ethanol-Induced Locomotion

Examination of ethanol-induced locomotion also identified the catecholamines as subserving this behavioral effect. For example, injection of AMPT blocks the locomotor stimulation produced by ethanol injection (Carlsson *et al*, 1972). In addition, depletion of forebrain NE with intracerebral injections of 6-OHDA exacerbates the locomotor suppressant effect of ethanol (Mason *et al*, 1979). Finally, administration of a moderate dose of ethanol produces an initial decrease, but a subsequent increase, in locomotor behavior. The initial locomotor decrease appears to be mediated by βARs, as the βAR antagonist, propranolol, selectively blocks the locomotor inhibition. The locomotor activation produced by ethanol later in the cycle, on the other hand, is blocked by phentolamine, an αAR antagonist (Matchett and Erickson, 1977).

NE and Ethanol CPP

There are no published studies examining the potential role of NE in the mediation of ethanol CPP.

NE and Ethanol SA: A Reassessment

New results reinforce the idea that NE contributes to the primary rewarding effects of ethanol. DBH knockout mice demonstrate a reduced voluntary ethanol consumption (Weinshenker *et al*, 2000), and while this reduction may result from a deficit in ethanol reward, it also may be due to the increased sensitivity of these mice to ethanol's aversive effects, such as sedation and hypothermia (Weinshenker *et al*, 2000). Another study showed that reducing NE transmission via activation of the α2AR autoreceptor with lofexidine attenuates alcohol SA, whereas increasing NE via blockade of this receptor enhances alcohol SA (Le *et al*, 2005). Finally, like stress-induced reinstatement of psychostimulants and opiates, relapse to ethanol-seeking behavior following footshock is attenuated by an α2AR agonist (Le *et al*, 2005).

PART III: DOPAMINE-DEPENDENT AND -INDEPENDENT MEDIATION OF DRUG ADDICTION BY NE

Although it is clear that NE signaling is important for at least some aspects of drug addiction, including primary reward, the underlying mechanisms have yet to be fully elucidated. In the present section we will discuss whether the effects of NE on responses to drugs of abuse depend on interactions with the DA system.

Control of Dopamine Neuron Firing and Dopamine Release by NE

Because DA is critical to many aspects of drug reward, understanding how NE influences DA signaling is of the

utmost importance. The mesolimbic and mesocortical DA systems, comprised of projections from the ventral tegmental area (VTA) to the NAc and PFC, respectively, receive noradrenergic innervation and are modulated by NE. A wiring diagram of the functional interactions between the noradrenergic and dopaminergic systems is shown in Figure 1. Noradrenergic neurons from the LC, A1, and A2 nuclei innervate the VTA (Jones *et al*, 1977; Simon *et al*, 1979; Liprando *et al*, 2004) and provide excitatory drive to midbrain DA neurons. Electrical stimulation of the LC induces burst firing of VTA neurons, whereas burst firing is blocked by the $\alpha_1$adrenoreceptor (α_1AR) antagonist, prazosin (Grenhoff *et al*, 1993; Grenhoff and Svensson, 1993). Conversely, lesions of the LC decrease striatal DA neuron activity (Tassin *et al*, 1979) and DA release (Russell *et al*, 1989; Lategan *et al*, 1990; Lategan *et al*, 1992). The PFC, a brain region implicated in responses to psychostimulants, also receives dense noradrenergic input from the LC (Swanson and Hartman, 1975; Morrison *et al*, 1981), which then sends excitatory glutamatergic projections to dopaminergic VTA neurons—though this connection may involve another glutamatergic relay nucleus (Carr and Sesack, 2000). Finally, the VNB projects directly to the NAc (Berridge *et al*, 1997; Delfs *et al*, 1998; Tong *et al*, 2006). These results form the basis of a functional connection between the noradrenergic and dopaminergic systems that is a likely component of central responses to drugs of abuse. Which (if any) of these circuits underlies the effects of NE on drug responses?

For the psychostimulants, results from multiple studies have demonstrated that the LC-PFC projection is critical for DA release in the NAc. A selective lesion of PFC NE abolishes both amphetamine-induced (Ventura *et al*, 2003) and morphine-induced (Ventura *et al*, 2005) DA release in the mouse NAc. Again, the α1AR appears to be the primary mediator of this effect. α_1Adrenoreceptor activation excites PFC pyramidal neurons (Marek and Aghajanian, 1999), and local infusions of prazosin (an α1AR antagonist) directly into the PFCs of rats blocks 'functional' DA release in the NAc (ie, the DA release associated with a behavioral response; Blanc *et al*, 1994; Darracq *et al*, 1998). Amphetamine-induced DA release in the NAc is also abolished in α1bAR knockout mice and in DBH knockout mice that lack NE (Auclair *et al*, 2002; Schank *et al*, 2006). Because the treatments that attenuate DA release in the NAc also attenuate psychostimulant-induced locomotion and CPP, the behavioral responses to psychostimulants appear to depend on NE activation of α1ARs in the PFC, which in turn promotes DA neuron firing and DA release in the ventral striatum.

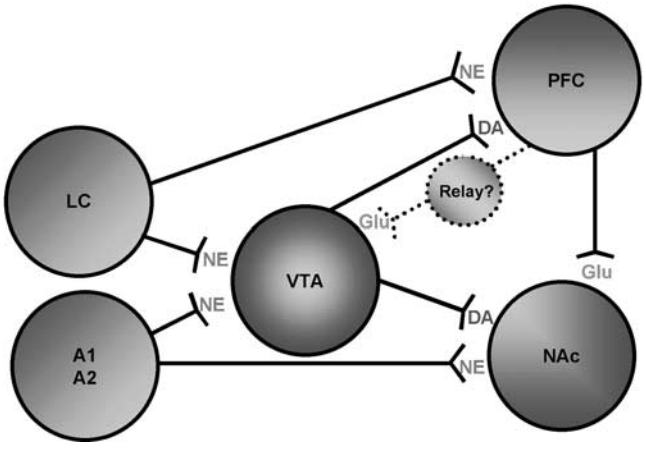

Figure 1 A wiring and neurotransmitter model for noradrenergic influence of psychostimulant responses. A1 and A2, brainstem noradrenergic cell groups; LC, locus coeruleus; PFC, prefrontal cortex; VTA, ventral tegmental area; NAc, nucleus accumbens; NE, norepinephrine; DA, dopamine; Glu, glutamate. Psychostimulant administration increases extracellular DA in the NAc and PFC and NE in the VTA, PFC, and NAc. NE signaling in the VTA induces burst firing of dopaminergic VTA neurons and increases DA release in the NAc. NE signaling in the PFC activates pyramidal neurons, which release Glu in the VTA resulting in increased excitability and more DA release in the NAc. Many of these noradrenergic inputs are mediated by the α1AR. The convergence of these signals in the NAc and PFC leads to psychostimulant-induced behaviors via downstream neuronal networks. Other cortical and subcortical inputs are also likely involved in the processes underlying addiction development, maintenance, and relapse.

The importance of the direct noradrenergic projections to the VTA and NAc has not been extensively studied, at least not directly (eg, by depleting NE or infusing AR antagonists locally into these regions and assessing drug reward, locomotion, etc). Nonetheless, there are some indications that these pathways are also important. Infusion of either DA or NE directly into the NAc stimulates locomotor activity in the rat, whereas local infusion of haloperidol attenuates the effects of both catecholamines (Pijnenburg *et al*, 1975; Svensson and Ahlenius, 1982). Furthermore, infusion of the α1AR antagonist, prazosin, into the NAc attenuates DA release in rats (Sommermeyer *et al*, 1995) and reduces the locomotor activity of mice in a novel environment (Stone *et al*, 2004). Although α1ARs are detectable in the NAc using radioligand binding, α1AR mRNA has not been found in accumbal neurons (Rainbow and Biegon, 1983; Day *et al*, 1997; Domyancic and Morilak, 1997). This somewhat limited set of results suggests that NE facilitates DA release and locomotor activity via α1ARs located on DA neuron terminals. Blockade of βARs with propranolol was reported to increase accumbal DA release and cocaine-induced locomotor activity, although the propranolol was administered peripherally, therefore the anatomical localization of these effects could not be pinpointed (Harris *et al*, 1996). In slice experiments, Nicola and Malenka (1998) reported that, like DA, NE depresses excitatory postsynaptic potentials in the NAc via an αAR-dependent mechanism. Although they did not 'localize' this effect, their data suggest that NE influences the activity of accumbal neurons directly. Because they used a nonselective αAR blocker (phentolamine), and as accumbal neurons do not express α1AR mRNA, the depression of EPSPs observed in this study is likely mediated by the α2AR, which is highly expressed in the striatum. The effects of accumbal infusion of adrenergic agonists/antagonists on drug-induced DA release and behavior have not been assessed. It would also appear that there is some reciprocal modulation of accumbal NE release by DA. Vanderschuren *et al* (1999) reported that D1 receptor activation facilitates, whereas D2 receptor activation depresses, accumbal NE release in slice culture.

The data on direct noradrenergic modulation of VTA DA neurons are also somewhat difficult to interpret, but quite

enticing. Although much of the work has focused on α1AR modulation of VTA DA neurons' firing properties, neither radioligand binding nor mRNA *in situ* hybridization techniques has reliably detected α1ARs in the VTA (Jones *et al*, 1985; Palacios *et al*, 1987; Pieribone *et al*, 1994). Thus, it is important to bear in mind that, until more sensitive techniques (eg, single-cell RT-PCR, electron microscopy) are employed to identify the exact anatomical localization of α1ARs in the VTA, many of the following conclusions remain speculative. In the mid-1990s, Grenhoff *et al* published a landmark series of studies examining modulation of DA cells by NE. In anesthetized rats, stimulation of the LC increases burst firing of VTA DA neurons, whereas decreasing NE release with an α2AR agonist or blocking α1ARs with prazosin will eliminate bursting and regularize the firing of these cells (Grenhoff and Svensson, 1989, 1993; Grenhoff *et al*, 1993). However, because the noradrenergic drugs were administered systemically, their effects could not be localized. The researchers went on to reexamine these effects in slice culture and found that α1AR activation has two effects—it both depolarizes DA cells and increases the frequencies of inhibitory postsynaptic potentials. The former effect was localized to DA neurons, because blocking synaptic transmission with tetrodotoxin (TTX) had no impact, whereas the latter effect was TTX sensitive and was attributed to the excitation of interneurons resulting in GABA release onto DA neurons (Grenhoff *et al*, 1995). This work has been ongoing the past few years and was eventually extended to include the effects of amphetamine on DA neuron activity. As with previous reports, Shi *et al* (2000) found that amphetamine depresses VTA DA neuron firing *in vivo*, primarily via D2 autoreceptor activation. However, when D2 receptors are blocked, the inhibitory effects of amphetamine switch to an α1AR-mediated excitation of these cells (increased firing rate and bursting). They went on to show that, even in the absence of D2 blockade, α1AR activation is responsible for the increase in the psychostimulant-induced augmentation of the slow oscillation firing pattern in VTA cells (Zhou *et al*, 2006). Again, as prazosin was administered peripherally in these experiments, localization of the α1AR effect could not be determined. Some of the most compelling data indicating a direct NE effect on VTA DA neurons is that, in slice culture, activation of α1ARs increases amphetamine-induced DA neuron activity by counteracting the inhibitory effect of mGluR1 activation (Paladini *et al*, 2001). This effect is likely due to direct action on DA neurons, both because the noradrenergic drugs were applied iontophoretically rather than superfused in the bath, and because the effects persisted in the presence of TTX and in the absence of Ca^{2+}. Interestingly, Paladini *et al* also identified a direct, α1AR-mediated *inhibitory* effect on DA neurons (Paladini and Williams, 2004). Thus, it would appear that α1AR activation excites as well as inhibits midbrain DA neurons. In the absence of pharmacological intervention, these cells typically have a bimodal spontaneous firing pattern: bursts —which greatly enhance DA release in the NAc—followed by periods of quiescence, when DA release is low or absent, and high variability in the interspike interval (Gonon, 1988; Bean and Roth, 1991; Grenhoff and Svensson, 1993). When noradrenergic transmission is blocked, both the excitatory and inhibitory effects of NE vanish, resulting in a regularization of DA neuron firing, and overall decreased DA utilization (Anden *et al*, 1970; Anden and Grabowska, 1976; Grenhoff and Svensson, 1989, 1993; Zhou *et al*, 2006). This regularization is critical because, as Tassin, Puglisi-Allegra, and others have shown, regularized DA release in the NAc is not functional in a behavioral sense; 'functional' DA release, which is characterized by the highly variable burst-quiescence pattern that is correlated with behavioral change, is largely dependent on α1AR activation (Darracq *et al*, 1998; Auclair *et al*, 2002). These results could explain why genetic or pharmacologic blockade of α1AR signaling attenuates amphetamine-induced DA release in the NAc and behavioral responses to psychostimulants. We are proposing a model in which fine tuning of DA neuron firing and accumbal DA release by combined NE signaling in the VTA, NAc, and PFC is critical for psychostimulant-associated behaviors.

Paradoxical Hyperdopaminergic State Following Chronic NE Depletion: Lessons from Dopamine β-Hydroxylase Knockout Mice

In the preceding sections, we reviewed literature demonstrating that NE, primarily via α1AR signaling, is required for proper DA neuron firing, DA release in the NAc, and psychostimulant-induced locomotion, sensitization, and CPP. These studies all shared a common feature: the blockade of NE signaling that led to depression of DA transmission and attenuation of psychostimulant-induced behaviors was either acute (eg, single exposure to prazosin) or involved just a single receptor subtype (eg, α1b knockout mice). We initiated a series of studies that aimed to elucidate the effects of chronic NE depletion on DA transmission and psychostimulant responses by using DBH knockout (*Dbh* −/−) mice, which lack NE completely from birth (Thomas *et al*, 1995; 1998). Understanding the effects of chronic NE depletion is important for several reasons. First, drug addiction is a chronic disease. Second, the proclivity to drug addiction is influenced by genetic variation that is in play throughout development and adulthood. Finally, any pharmacological intervention used to treat addiction will be chronic of necessity.

We predicted that the behavior of *Dbh* −/− mice would mirror that of prazosin-treated mice or α1bAR knockout mice. Surprisingly, instead of an attenuated response to psychostimulants, *Dbh* −/− mice are hypersensitive to the locomotor, rewarding, and aversive effects of cocaine and amphetamine (Weinshenker *et al*, 2002a; Schank *et al*, 2006). To explain the underlying mechanisms of this paradoxical hypersensitivity to psychostimulants on the part of *Dbh* −/− mice, we examined DA transmission by microdialysis and radioligand binding. We found that *Dbh* −/− mice have a reduction in basal extracellular DA in the NAc and CP, whereas amphetamine-induced DA release is abolished in the NAc and attenuated in the CP and PFC (Schank *et al*, 2006; Seeman *et al*, 2005). It is important to note that the 'ectopic' DA produced in 'noradrenergic' neurons in *Dbh* −/− mice is not the cause of the hypersensitivity; although *Dbh* −/− mice indeed *produce* more DA in brain tissue than normal mice (Thomas *et al*, 1998; Bourdelat-Parks *et al*, 2005), overall DA release is

hampered. These results are consistent with those discussed in the previous section demonstrating that NE is important for DA neuron activity and DA release. It has been well established that the DA system compensates for a loss of dopaminergic tone by upregulating DA receptor signaling capacity, and that is exactly what happens in *Dbh* −/− mice. Using radioligand binding in the presence and absence of guanine nucleotide, which can discriminate between low- and high-affinity state DA receptors, we found that the density of high-affinity state DA receptors is increased three to to six-fold in the NAc and CP of *Dbh* −/− mice (Seeman *et al*, 2005; Schank *et al*, 2006). Furthermore, *Dbh* −/− mice are behaviorally hypersensitive to quinpirole, a direct D2 agonist (Weinshenker *et al*, 2002a). Thus, when NE is blocked acutely, DA transmission and behavioral responses to psychostimulants appear to be attenuated. In contrast, when NE is blocked chronically, a similar attenuation in DA release occurs, but over time the DA system compensates by upregulating high-affinity state postsynaptic DA receptors, which results in a behavioral hypersensitivity to psychostimulants. In support of this hypothesis, other treatments that result in long-term NE depletion (eg, neurotoxic lesions of the LC or chronic treatment with a DBH inhibitor) also produce hypersensitivity to psychostimulants and direct DA agonists (Donaldson *et al*, 1976; Lategan *et al*, 1990; Harro *et al*, 2000). We will revisit this model when we discuss the current and potential uses of DBH inhibitors for treating cocaine dependence.

Nontraditional NE–DA Interactions

Besides the important influence of NE transmission on DA signaling, the noradrenergic system can influence the dopaminergic system in at least three 'nontraditional' ways: uptake of DA by noradrenergic neurons, release of DA by noradrenergic neurons, and activation of adrenergic receptors by DA.

The plasma membrane NET, which is responsible for the uptake of extracellular NE, is also capable of transporting DA *in vitro* (Raiteri *et al*, 1977). This raises the possibility that the NET may be at least partially responsible for DA uptake in brain regions innervated by both DA and NE neurons. This is an especially intriguing hypothesis, because the ability of selective DAT blockers to increase extracellular DA concentrations is oddly low in certain brain regions, such as the PFC (Carboni *et al*, 1990; Di Chiara *et al*, 1992). Indeed, further studies by a number of groups using selective transporter blockers and transporter knockout mice confirmed that the NET is primarily responsible for DA uptake in the PFC, where DAT is scarce, and significantly contributes to DA uptake in regions where NET and DAT coexist, such as the NAc shell and BNST (Mundorf *et al*, 2001; Moron *et al*, 2002; reviewed by Carboni and Silvagni, 2004). These results indicate that the psychostimulant-induced increase in extracellular DA in the PFC is mediated predominantly by NET and not DAT blockade. In addition, when DAT is impaired (eg, DAT knockout mice), the NET may represent the primary mechanism for DA uptake in other brain regions. Interestingly, nisoxetine, a selective NET blocker, cannot support a CPP in normal mice, but it can in DAT heterozygote and knockout mice (reviewed by Uhl *et al*, 2002).

DA is synthesized by all NE neurons and is converted to NE by DBH during NE biosynthesis. Under normal conditions, tyrosine hydroxylase—not DBH—is rate limiting for NE synthesis (reviewed by Udenfriend, 1966). However, the conversion of DA to NE may not be completely efficient, and DBH can become rate limiting when neuronal activity is high or when DBH is genetically compromised or pharmacologically inhibited. Under these conditions (and perhaps others) 'noradrenergic' neurons do appear to release DA (Scatton *et al*, 1984; Devoto *et al*, 2001; Weinshenker *et al*, 2002b; Carboni and Silvagni, 2004; Bourdelat-Parks *et al*, 2005; Devoto *et al*, 2005).

Because DA is structurally similar to NE, DA can activate cloned ARs in cell culture, although with less potency than NE by 2–3 orders of magnitude (eg, Zhang *et al*, 2004). Paladini *et al*, 2001 showed that the ability of NE to activate α1ARs in VTA neurons in brain slices is recapitulated by DA. Debate has swirled for years around the issue of whether DA can activate α1ARs—although some evidence exists in the affirmative, alternative explanations can often undercut its persuasiveness. In addition, work with *Dbh* −/− mice has indicated that DA cannot activate α1ARs *in vivo*. For example, if DA *could* activate α1ARs, *Dbh* −/− mice would be expected to: lack phenotypes consistent with the absence of α1ARs; lack phenotypes that could be rescued by an α1AR agonist; and respond to α1AR antagonists. On the contrary, *Dbh* −/− mice do have reductions in DA release consistent with an absence of α1ARs (Schank *et al*, 2006); they also have a seizure susceptibility phenotype that is rescued by an α1AR agonist (Weinshenker *et al*, 2001) and are completely indifferent to the α1AR antagonist, prazosin (Weinshenker *et al*, 2002a). Currently, activation of an AR by DA *in vivo* is supported by good evidence in just one instance: α2cARs in the striatum. Given the relatively sparse noradrenergic innervation of the striatum (Lindvall and Björklund, 1974; Swanson and Hartman, 1975), there is a surprising abundance of α2ARs in this region, especially the α2cAR (Ordway *et al*, 1993; Nicholas *et al*, 1993; Uhlen *et al*, 1997). This paradox led Ordway *et al* to propose that DA, rather than NE, is the endogenous ligand for α2cARs in the striatum (Zhang *et al*, 1999). They showed that activation of cloned α2cARs with either NE or DA inhibits forskolin-induced cAMP accumulation (Zhang *et al*, 1999) and that α2cAR activation inhibits GABA release in striatal slices (Zhang and Ordway, 2003). Thus, DA activation of these 'adrenergic' receptors may be a normal component of striatal DA signaling and could modulate responses to drugs of abuse.

Some Effects of NE on Drug Responses may be Independent of DA

Although the effects of noradrenergic manipulations on psychostimulant responses appear to be primarily mediated by the modulation of DA release, some of the mechanisms by which NE influences opiate and ethanol reward may be independent of DA. The criteria for this putative DA-independent pathway are that manipulations of NE function alter drug responses, whereas DA manipulations are without consistent effect. For example, *Dbh* −/− and α1bAR knockout mice do not develop morphine CPPs, indicating

that normal NE function is critical for opiate-conditioned reward (Olson *et al*, 2006; Drouin *et al*, 2002), whereas DA-deficient mice display normal CPP acquisition (Hnasko *et al*, 2005). In addition, intra-NAc infusion of a broad-spectrum DA antagonist has no effect on morphine CPP in drug-naïve animals (Laviolette *et al*, 2002). A possible anatomical substrate for these potential DA-independent effects is the direct NE projection of the VNB to the NAc (Berridge *et al*, 1997; Delfs *et al*, 1998; Tong *et al*, 2006), a hypothesis buttressed by the fact that 6-OHDA lesions of accumbal DA (NE content was unaffected in this particular study) selectively attenuate cocaine SA, but not heroin SA, in rats (Pettit *et al*, 1984), whereas kainic acid lesions of the same structure disrupt both cocaine and heroin SA (Zito *et al*, 1985). Together, these data suggest that other neurotransmitters in the NAc, such as NE, mediate the primary reinforcing effects of opiates. Other potential neuroanatomical candidates are the PFC, amygdala, and BNST, which receive direct noradrenergic input and modulate various aspects of drug reward and addiction. One important caveat—the negative DA findings are inconsistent with other reports demonstrating that DA antagonism prevents opioid CPPs and SA (reviewed by Bardo and Bevins, 2000; McBride *et al*, 1999; Tzschentke, 1998; Bardo, 1998). However, these studies are complicated by the aversive and memory-impairing properties of DA receptor antagonists themselves.

Noradrenergic manipulations that alter ethanol intake may also occur independently of DA function. For example, chemical lesions of the NE system, blocking NE synthesis via DBH inhibitors, or genetic deletion of DBH will reduce voluntary ethanol intake, whereas DA lesions do not (Brown *et al*, 1977; Kiianmaa *et al*, 1979; Rassnick *et al*, 1993b; Weinshenker *et al*, 2000). Again, evidence does suggest that pharmacologic or genetic manipulation of D1 and D2 receptors can modulate ethanol SA in some circumstances (Weiss *et al*, 1990; Hubbell *et al*, 1991; Dyr *et al*, 1993; Rassnick *et al*, 1993a; Ng and George, 1994; Silvestre *et al*, 1996; Cohen *et al*, 1998, 1999; El-Ghundi *et al*, 1998; Phillips *et al*, 1998; Risinger *et al*, 2000; Boyce and Risinger, 2002; D'Souza *et al*, 2003; Zocchi *et al*, 2003). Further research teasing out the specific mechanisms of noradrenergic modulation of opioid and ethanol reward will be required to distinguish between DA-dependent and DA-independent pathways.

PART IV: INFLUENCE OF NORADRENERGIC GENE POLYMORPHISMS AND NORADRENERGIC PHARMACOTHERAPY ON DRUG DEPENDENCE

Addiction researchers have invested tremendous effort over the years to develop pharmacotherapies for drug dependence. In general, these potential therapies act by one of the following means: reducing drug reward, increasing drug aversion, or partially substituting for the abused drug. Results for each strategy have been mixed, ranging from substantial success (eg, methadone/buprenorphine maintenance for opiate dependence) to general failure (eg, DA agonists/antagonists for cocaine dependence). In this section, we will review the efficacy of noradrenergic compounds in the treatment of drug addiction.

Disulfiram and Cocaine Dependence

At the present time, disulfiram has shown probably the greatest promise of any compound for the treatment of cocaine addiction. Disulfiram (Antabuse®) has been used for over 50 years in the treatment of alcoholism (Fuller *et al*, 1986). Disulfiram inhibits the enzyme aldehyde dehydrogenase, which results in the accumulation of acetaldehyde, a toxic metabolic intermediate, upon ethanol ingestion. Acetaldehyde produces 'the Antabuse reaction', an aversive syndrome characterized by flushing, nausea, and vomiting. The desire to avoid this syndrome by reducing alcohol intake is believed to be responsible for the reductions in alcohol use in dependent individuals.

The idea of using disulfiram to treat cocaine addiction originates from the remarkable degree of comorbidity seen with alcohol dependence and cocaine dependence (Regier *et al*, 1990; Carroll *et al*, 1993; Higgins *et al*, 1993). Although preliminary findings indeed supported the efficacy of disulfiram in cocaine/alcohol codependent individuals (Carroll *et al*, 1998, 2000), results from three recent studies strongly suggest that comorbid alcohol use is not necessary for disulfiram treatment of cocaine dependence—in fact, nonalcohol-dependent subjects may derive even more benefit from disulfiram treatment than those who also abuse alcohol (George *et al*, 2000; Petrakis *et al*, 2000; Carroll *et al*, 2004). Because the drug combination of disulfiram and cocaine in the absence of alcohol does not result in acetaldehyde accumulation, the reduction of cocaine use with disulfiram treatment must depend on an interaction other than inhibition of aldehyde dehydrogenase.

As it happens, disulfiram is also a potent inhibitor of DBH. Most inhibitors of DBH, including disulfiram, chelate copper, thus depriving DBH of its required cofactor (Goldstein *et al*, 1964). Disulfiram inhibits DBH in animals, decreasing NE and increasing DA in both peripheral and central tissues (Musacchio *et al*, 1966; Karamanakos *et al*, 2001). In humans, disulfiram decreases NE and its metabolites in urine, blood, and cerebrospinal fluid (Takahashi and Gjessing, 1972; Major *et al*, 1979; Rogers *et al*, 1979; Hoeldtke and Stetson, 1980; Rosen and Lobo, 1987; Paradisi *et al*, 1991). Disulfiram inhibits DBH and aldehyde dehydrogenase similarly, with IC_{50} values in the low (μM) range for both enzymes (Green, 1964; Mays *et al*, 1998). Because the rewarding and aversive effects of cocaine are primarily mediated by NE and DA, we (along with others) have proposed that DBH inhibition is likely a key to the success of disulfiram treatment for cocaine dependence (McCance-Katz *et al*, 1998a, b; George *et al*, 2000; Petrakis *et al*, 2000; Bourdelat-Parks *et al*, 2005; Schank *et al*, 2006; Sofuoglu and Kosten, 2006).

Because the treatment of alcoholism with disulfiram appears to depend on the drug's ability to create an aversive reaction to alcohol ingestion, a similar mechanism, mediated by DBH inhibition, may be responsible for its effect on cocaine dependence. But is there evidence to support such a mechanism of action? First, we point out that *Dbh* −/− mice have altered responses to cocaine. Perhaps of greatest significance, *Dbh* −/− mice display a conditioned place *aversion* to cocaine at doses that normally support a *CPP* in regular mice (Schank *et al*, 2006). In humans, a common polymorphism (allele frequency of

0.22) that accounts for much of the genetic variance in DBH activity was identified in the promoter region of the human DBH gene (C–T change at nucleotide position −1021) (Zabetian *et al*, 2001). CT heterozygotes have levels about 50% lower than those found in CC homozygotes, whereas TT homozygotes have very low DBH activity (~10% of CC). Also of note, individuals receiving disulfiram treatment have reported a higher incidence of paranoia associated with cocaine use than those not receiving disulfiram (Hameedi *et al*, 1995; McCance-Katz *et al*, 1998a, b), and individuals with genetically low DBH activity appear to be particularly susceptible to cocaine-induced paranoia (Cubells *et al*, 2000; R Malison, personal communication). Finally, there appears to be a pharmacogenetic interaction between disulfiram and DBH genotype. The effects of disulfiram and DBH mutations on catecholamine levels are additive in mice (Bourdelat-Parks *et al*, 2005), and individuals with low DBH activity are more susceptible to some aversive side effects of disulfiram, including psychosis (Heath *et al*, 1965; Ewing *et al*, 1977; Major *et al*, 1979) and sedation (Ewing *et al*, 1978). In a recent genotype-controlled pilot study, disulfiram effectively reduced cocaine intake only in individuals carrying at least one low-activity DBH allele (Cubells *et al*, 2000). Together, these combined results suggest the existence of a second aversive 'Antabuse reaction' that promotes cocaine abstinence and that is mediated by inhibition of DBH, not aldehyde dehydrogenase. Because blockade of NE signaling attenuates footshock-induced and cocaine-primed reinstatement of cocaine seeking in rats, an attenuation of factors that cause relapse, such as stress or drug exposure, could also contribute to the success of disulfiram. The next step, clearly, is to test the efficacy of *selective* DBH inhibitors in preclinical models of cocaine addiction and in cocaine-dependent individuals, preferably in a manner that will take DBH genotype into account. The possibility that disulfiram and other DBH inhibitors may be effective in treating dependence to other psychostimulants, such as methamphetamine, also merits exploration.

Other Noradrenergic Compounds Affecting Drug Abuse

Although disulfiram is the most promising noradrenergic treatment for drug dependence, there are others that have met with some success. NET blockers, such as desipramine and reboxetine, have been modestly effective in treating cocaine addiction (Kosten *et al*, 2005; McDowell *et al*, 2005; Szerman *et al*, 2005), although this may have more to do with their antidepressant activity than with a direct effect on cocaine responses, *per se*. One recent set of studies reported that the wake-promoting drug, modafinil, which is approved as a treatment for narcolepsy, was able to reduce cocaine intake in a dependent cohort (Dackis *et al*, 2003; 2005). Intriguingly, modafinil inhibits both DAT and NET, and both its locomotor and wake-promoting effects are attenuated by α1AR blockade in rodents and nonhuman primates (Duteil *et al*, 1990; Hermant *et al*, 1991; Stone *et al*, 2002; Madras *et al*, 2006). Perhaps its efficacy in treating cocaine dependence is also tied to α1AR signaling, although influences on glutamatergic transmission are another possibility (Ferraro *et al*, 1999; Dackis and O'Brien, 2003).

There were a few reports from the 1970s indicating that propranolol, a βAR antagonist, could block the euphoric effects of opiates and might be effective in treating opiate dependence in human addicts (Grosz, 1972). Moreover, subsequent preclinical research suggested that propranolol could attenuate some of the behavioral effects of morphine in rats (Black and Grosz, 1974; Black *et al*, 1975). However intriguing, the importance of this line of research was called into question, as subsequent studies were unable to replicate the original claim that propranolol could attenuate the euphoric effects of opiates in humans, and the issue has not been taken up again (Jacob *et al*, 1975; Resnick *et al*, 1976).

DBH and Alcoholism

As described previously, disulfiram inhibits aldehyde dehydrogenase, which results in the accumulation of a toxic metabolic intermediate—acetaldehyde—upon ethanol ingestion. Acetaldehyde produces the aversive symptoms that are presumed responsible for reductions in ethanol intake. Because disulfiram inhibits DBH and aldehyde dehydrogenase to a similar degree (Green, 1964; Mays *et al*, 1998), it is possible that disulfiram inhibition of DBH may be partly responsible for the reduction of ethanol ingestion following disulfiram administration. Amit *et al* (1976) examined this possibility by determining the efficacy of calcium carbimide, FLA-63, and disulfiram in decreasing ethanol intake and the effect each of these compounds had on acetylaldehyde levels following ethanol injection. Of the three compounds tested, calcium carbimide had the greatest effect on acetylaldehyde levels following ethanol injection, but the least effect on ethanol intake. Administration of disulfiram and FLA-63 (both DBH inhibitors) significantly reduced ethanol intake. Of the two compounds, FLA-63 had the least effect on acetylaldehyde levels, but was the most potent suppressor of ethanol intake. This series of results led the authors to conclude that disruption of NE synthesis may significantly contribute to the efficacy of disulfiram in the treatment of alcoholism.

DBH function has also been implicated in human alcoholism. Plasma DBH activity in alcoholic subjects is lower than that seen in nonalcoholics (Kohnke *et al*, 2002), and alcoholics have an increased frequency of the low-activity A allele of the DBH(*) 444G/A polymorphism (Kohnke *et al*, 2006). These studies indicate that the genetic determinants of DBH function may be associated with alcoholism. This is why pharmacological remediation with NE modulators may represent a rational therapeutic treatment strategy for alcohol abuse.

CONCLUSION

Although NE was dismissed as a key player in reward and addiction during the mid-1970s, more recent work has given us pause and led us to rethink the importance of this neurotransmitter. As always, it is a marvel how similar data can be perceived and interpreted so differently. When researchers discovered that DA is dispensable for opiate and ethanol SA and CPP for a number of addictive compounds, the general conclusion was that there had to be both

DA-dependent *and* DA-independent reward pathways. In marked contrast, when NE was deemed unimportant for the maintenance phase of psychostimulant SA, it was dismissed as having no role in addiction at all—this despite the fact that NE *does* appear to be necessary for voluntary ethanol consumption, CPP for psychostimulants and opiates, and stress-induced reinstatement of multiple drugs of abuse. We propose that, as with DA, there are both NE-dependent and NE-independent circuits that influence drug response and addiction parameters. Further, some of the NE-dependent pathways (like those related to psychostimulant-induced behaviors) are mediated by the modulation of DA release, whereas others (eg, ethanol SA, opiate CPP) may not be.

To obtain a comprehensive picture of the role NE actually plays in drug reward and addiction, a number of important questions need to be addressed. What is the anatomical location for the influence of NE on ethanol reward? Is NE important for opiate SA? What is the exact role of NE release in the NAc and VTA in drug-induced behaviors? Do VTA neurons express adrenergic receptors (especially α1ARs), and if so, what types? Do functional polymorphisms in DBH and other genes in the noradrenergic pathway modulate aspects of addiction? Is the mechanism of disulfiram-induced cocaine abstinence really DBH inhibition? Finding answers to these questions will enhance our knowledge of reward and addiction pathways and may lead to novel treatments for drug dependence.

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