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Monoamine transporters and psychostimulant addiction

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ABSTRACT

Psychostimulants are a broadly defined class of drugs that stimulate the central and peripheral nervous systems as their primary pharmacological effect. The abuse liability of psychostimulants is well established and represents a significant public health concern. An extensive literature documents the critical importance of monoamines (dopamine, serotonin and norepinephrine) in the behavioral pharmacology and addictive properties of psychostimulants. In particular, the dopamine transporter plays a primary role in the reinforcing and behavioral-stimulant effects of psychostimulants in animals and humans. Moreover, both serotonin and norepinephrine systems can reliably modulate the neurochemical and behavioral effects of psychostimulants. However, there is a growing body of evidence that highlights complex interactions among additional neurotransmitter systems. Cortical glutamatergic systems provide important regulation of dopamine function, and inhibitory amino acid γ-aminobutyric acid (GABA) systems can modulate basal dopamine and glutamate release. Repeated exposure to psychostimulants can lead to robust and enduring changes in neurobiological substrates, including monoamines, and corresponding changes in sensitivity to acute drug effects on neurochemistry and behavior. Significant advances in the understanding of neurobiological mechanisms underlying psychostimulant abuse and dependence have guided pharmacological treatment strategies to improve clinical outcome. In particular, functional agonist treatments may be used effectively to stabilize monoamine neurochemistry, influence behavior and lead to long-term abstinence. However, additional clinical studies are required in order to identify safe and efficacious pharmacotherapies.

1. Introduction

The abuse liability of psychostimulants is well established and represents a significant public health concern. Cocaine is widely recognized as one of the most addictive and dangerous illicit drugs used. The most recent proceedings of the National Institute on Drug Abuse (NIDA) Community Epidemiology Work Group (CEWG), published in 2003, reported that cocaine and crack abuse was endemic in almost all 21 major United States metropolitan areas surveyed. Rates of emergency department visits per 100,000 population were higher for cocaine than for any other illicit drug in 17 areas, and trends in

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Abbreviations: GABA, γ-aminobutyric acid; NIDA, National Institute on Drug Abuse; CEWG, Community Epidemiology Work Group; ADHD, attention deficit hyperactivity disorder; SLC, solute carrier; MDMA, 3,4-methylenedioxymethamphetamine; SNP, single nucleotide polymorphism; VTA, ventral tegmental area; LC, locus coeruleus; VMAT, vesicular monoamine transporter; ERK1/2, extracellular signal-related kinases 1 and 2; RTI-336, 3β-(4-chlorophenyl)tropane-2β-[3-(4-methylphenyl)isoxazol-5-yl] hydrochloride; mGluR, metabotropic glutamate receptor; NAC, *N*-acetylcysteine; NMDA, *N*-methyl-D-aspartate; PET, positron emission tomography; FDG, 2-fluoro-2-deoxy-D-glucose; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid.

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treatment admissions from 2000 to 2002 showed little change in most areas surveyed. Methamphetamine use has increased dramatically. Between 1996 and 2002, the number of individuals who reported lifetime methamphetamine use increased by approximately 250%. Drug abuse related emergency department visits involving methamphetamine or amphetamine increased 54% in the United States between 1995 and 2002. Currently, no effective pharmacotherapy for psychostimulant abuse has demonstrated efficacy for long-term use. Clearly, a better understanding of the neuropharmacological effects of cocaine and related psychostimulants will support efforts to develop and improve useful pharmacotherapies for psychostimulant abuse.

An extensive literature documents the critical importance of monoamines (dopamine, serotonin and norepinephrine) in the behavioral pharmacology and addictive properties of psychostimulants. In particular, dopamine plays a primary role in the reinforcing and behavioral-stimulant effects of psychostimulants in animals and humans. Although the reinforcing and behavioral-stimulant effects of psychostimulants do not appear to depend directly on serotonin, the results of drug interaction studies clearly demonstrate that pharmacological modulation of the serotonin system can reliably alter the behavioral and neurochemical effects of psychostimulants. Similarly, norepinephrine does not appear to play a significant role in the reinforcing effects of psychostimulants but drugs that increase norepinephrine can share interoceptive effects with psychostimulants as evidenced by drug discrimination studies. Recent evidence also implicates norepinephrine in stress- and drug-induced reinstatement of extinguished psychostimulant self-administration. Finally, there is a growing body of evidence that highlights complex interactions among additional neurotransmitter systems. Cortical glutamatergic systems provide important regulation of dopamine function. Similarly, GABA systems provide inhibitory neuromodulation of monoaminergic and glutamatergic function. Drug abuse and addiction is a highly complex behavioral disorder. It is not surprising that the neurobiological substrates underlying psychostimulant abuse and dependence involve a complex interplay among multiple neurotransmitter systems.

It is important to emphasize that a number of synthetic stimulants, including amphetamines, are useful medications in the treatment of attention deficit hyperactivity disorder (ADHD), narcolepsy, excessive daytime sleepiness and obesity. Cocaine is still used clinically as a local anesthetic, primarily for eye, ear, nose or throat procedures. Some examples of stimulant medications legally available in the United States and their medical indications are provided in Table 1. Most of these drugs are analogs of the basic phenethylamine chemical structure closely related to the catecholamine neurotransmitters, norepinephrine and dopamine. The present review will focus primarily on the neuropharmacology of cocaine, amphetamine and methamphetamine due to their high abuse potential as reflected in their categorization as Schedule II drugs (Federal Controlled Substances Act). Other stimulants have potential for abuse and dependence due to their similar profile of pharmacological effects. For example, it is well established that methylphenidate is diverted from legitimate sources, such as Ritalin, and is misused or abused by a segment of the United States population [1]. Also, there are a number of illicit amphetamine derivatives, including 3,4-methylenedioxymethamphetamine (MDMA, ''Ecstasy''), that have prominent stimulant and hallucinogenic properties. Recently, neurotoxicity associated with the use of amphetamine derivatives has been an area of intense investigation [2–4].

2. Biochemistry and regulation of monoamine transporters

Release, reuptake, and recycling of neurotransmitters at the synapse are regulated by neurotransmitter transport systems [5,6]. The transporter molecules for dopamine, serotonin, and norepinephrine are members of the sodium:neurotransmitter symporter family (SNF) [7]. These proteins are single polypeptide chains of 500–600 amino acids with 12 transmembrane alpha-helices with intracellularly oriented amino and carboxy termini [8,9]. Their structure has been confirmed with the crystallization of a bacterial solute carrier (SLC) 6 homologue that is a transporter of leucine [10]. These proteins act as co-transporters of sodium and chloride ions and of transmitter molecules [11]. Transporters use the cellular sodium gradient that is maintained by Na^+/K^+-ATPase [12]. Two sodium ions and one chloride ion are co-transported with each positively charged monoamine molecule [13].

Dopamine, serotonin and norepinephrine transporters are synthesized in the cell soma and transported to sites of utilization. In vivo studies using an irreversible dopamine and serotonin transporter inhibitor indicate that the half-lives of recovery from inactivation of these transporter proteins are 2 days [14–16] and 3.4 days [17], respectively. To our knowledge, no similar studies have been done to determine the half-life of the norepinephrine transporter protein. Alteration of cell surface expression of transporters is a mechanism for regulating monoamine transport. Post-translational modifications such as phosphorylation and glycosylation regulate transporter function and expression levels [18–21]. Amino acid sequence analyses of monoamine transporter proteins reveal numerous consensus sites for protein kinases as well as

Table 1 – Examples of psychostimulants used as therapeutics in the United States

Drug	Trade names	Medical indications
Amphetamine	Adderall®	ADHD, narcolepsy, weight control
	Dexedrine®	
	Dextrostat®	
Diethylpropion	Tenuate®	Weight control
Methamphetamine	Adipex®	ADHD, weight control
	Desoxyn®	
	Methedrine®	
Methylphenidate	Ritalin®	ADHD, narcolepsy
Phentermine	Adipex-P®	Weight control
	Fastin®	
	Ionamin®	

putative interactive motifs in cytoplasmic domains, suggesting that second messengers may be involved in these modifications [22]. Agents that activate protein kinase C or maintain phosphorylation states rapidly reduce monoamine transport without altering substrate affinity [19–21,23,24]. This reduction in transport arises from a loss in transporter cell surface expression [25–32]. In addition, extracellular substrates influence transporter phosphorylation and/or trafficking in a receptor-independent manner [33]. The dopamine transporter is phosphorylated on N-terminal serine residues [34], while determinants within the C-terminus of the norepinephrine transporter regulate its trafficking, stability, and activity [35]. The consensus sites for several kinases on the norepinephrine transporter protein are distinct from those present in the dopamine and serotonin transporter proteins, suggesting that the norepinephrine transporter may be regulated by mechanisms that are distinct from those of dopamine and serotonin transporters [22]. Consensus sites for glycosylation are located on the large second extracellular loop [36,37]. Transporters undergo a biosynthetic progression from non-glycosylated to core and higher-order glycosylation, with the most mature form inserted in the plasma membrane [36,38]. The correct trafficking of transporters from the endoplasmic reticulum to the plasma membrane also depends upon formation of oligomers [39,40]. Interactions between the transmembrane domains contributes to the formation of these oligomers [41–43]. Recent studies suggest that monoamine transporters are most likely organized in the plasma membrane as a tetramer, a dimer of dimers, and that their transport functionality is dependent upon these homo-oligomeric interactions [42,44,45].

Endogenous monoamines can also influence transporter protein trafficking and membrane insertion via the mechanisms described above. For example, increasing extracellular concentrations of dopamine decreased dopamine transport in rat striatal synaptosomes [46]. Recent cell culture studies indicate that activation of presynaptic dopamine D2 receptors with an agonist can rapidly elevate the surface expression and dopamine clearance capacity of the dopamine transporter via extracellular signal-related kinases 1 and 2 (ERK1/2) [47]. Serotonin controls protein kinase C-dependent serotonin transporter phosphorylation and surface distribution [33]. In addition, the rate of neurotransmitter transport is voltage-dependent such that the velocity is increased by hyperpolarization of the membrane and decreased by depolarization of the membrane [48–50].

Dopamine, serotonin and norepinephrine transporters each show specificity for their particular monoamine substrate [51]. However, monoamine transporter function can overlap in genetically altered mice that lack the function of one of these monoamine transporters [52–55]. In addition, norepinephrine transporters will transport molecules, such as dopamine, tyramine, and amphetamine, that are structurally similar to norepinephrine [56,57]. In the prefrontal cortex, where both norepinephrine and dopamine fibers are present, dopamine is taken up by the norepinephrine transporter [58,59].

Within the cell, vesicular transport systems concentrate neurotransmitter molecules in synaptic vesicles for additional cycles of release. The vesicular monoamine transporter (VMAT) is responsible for the translocation of monoamines from the cytoplasm into synaptic vesicles using a proton electrochemical gradient [60,61]. Although there is a lack of sequence homology between VMAT and the plasma membrane monoamine transporters, hydrophobicity analyses of rat VMAT sequences suggest a VMAT protein structure similar to that of the plasma membrane transporters, with 12 transmembrane domains, N- and C-termini in the cytosol, and glycosylation sites located on a large extracytosolic loop [62,63]. One notable structural difference is that the large extracytosolic loop is located between transmembrane domains 1 and 2 for VMAT, but between domains 3 and 4 for the plasma membrane transporters [5]. VMAT is functionally distinct from the sodium-dependent plasma membrane transporter in that monoamine transport is coupled to a proton gradient across the vesicle membrane [60,61]. VMAT2 plays an important role in neuroprotection, sequestering the neurotoxic by-products of oxidative deamination of monoamines within vesicles [64–66]. Unlike the plasma monoamine transporters, the vesicular transporters are nonspecific in that they transport all monoamine transmitters into vesicles with roughly the same affinity [67,68].

3. Localization and function of monoamine transporters

Monoamines play important roles in normal brain function and are implicated in various neuropsychiatric disorders, thus the regulation of these neurotransmitters is critically important. Dopamine is implicated in many physiological processes such as movement, cognition, memory, and reward [69]. The action of dopamine in the synapse is terminated by reuptake into presynaptic neurons via the dopamine transporter, which also serves to recycle neuronal dopamine, thus decreasing the need for newly synthesized dopamine [70,71]. Cell bodies that produce dopamine are localized to the substantia nigra (SN), the ventral tegmental area (VTA), and the hypothalamus. These project to the caudate nucleus, putamen, nucleus accumbens, and prefrontal cortex [72]. Dopamine transporter immunolabeling studies have revealed that the dopamine transporter is preferentially localized perisynaptically rather than in the synaptic component of the presynaptic membrane [73,74]. The dopamine transporter is expressed in all dopamine neurons, with the highest levels in neurons originating in the substantia nigra and VTA [75]. Serotonin is implicated in many functions, including mood, sleep, appetite, anxiety, fear, reward, and aggression [76,77]. Serotonin-producing neurons are restricted to the raphe nuclei in the brainstem, and project to the cortex, thalamus, basal ganglia, hippocampus, and amygdala [78]. High levels of serotonin transporter have been localized to the ventral striatum, bed nucleus of the stria terminalis, the amygdaloid complex, raphe nucleus, and the ventromedial hypothalamus of humans [79] and nonhuman primates [80]. Norepinephrine plays a critical role in arousal [81], attention, memory, and mood [82]. Norepinephrine is synthesized primarily in the locus coeruleus (LC) and surrounding nuclei in mammals, including humans [83]. In the human brain, the densest concentrations of the norepinephrine transporter are found in the LC and raphe complex,

with moderate levels in the hypothalamus, midline thalamic nuclei and the bed stria nucleus terminalis, and the lowest levels in the cortex, hippocampus and striatal regions [84]. Anatomical studies have shown consistently that monoaminergic neurons each express a specific plasma membrane transporter [85].

Adult human monoaminergic neurons in the central nervous system express only VMAT2, while VMAT 1 is predominantly expressed in neuroendocrine cells in the adrenal medulla and intestinal tract [86]. VMAT2 is found in dopamine cells localized to the dorsal premammillary nucleus, substantia nigra pars compacta and ventral tegmental area, in norepinephrine cell groups in the A5, LC, and subceruleus and in serotonin cell groups in the dorsal and median raphe and the raphe pallidus [87].

4. Genetics of monoamine transporters

Plasma membrane neurotransmitter transporters are composed of two structurally and mechanistically distinct gene families, the high-affinity glutamate transporters (SLC1 gene family) and the sodium/chloride coupled transporters (SLC6 gene family), the latter of which includes the transporters of monoamines (dopamine, serotonin, and norepinephrine) as well as transporters of glycine and GABA, amino acids, creatine, and osmolytes such as betaine and taurine [6,88]. Similarly, there are three subclasses of intracellular transporters: the vesicular amine transporter (SLC18 gene family), the vesicular inhibitory amino acid transporter (SLC32 gene family), and the vesicular glutamate transporter (SLC17 gene family) [89]. Two pharmacologically distinct VMAT isoforms, VMAT1 and VMAT2, have been cloned and described [62,63,90].

Since the cloning of many of the SLC6 family members, much work has been done to ascertain whether polymorphisms of these genes are linked to various behavioral traits, drug sensitivities, or disease susceptibilities. These genetic variations often result in altered transporter distribution and/or function, as described by a recent comprehensive review [88]. Several single nucleotide polymorphisms (SNP) of the human dopamine transporter gene (SLC6A3) have been identified, several of which have been associated with ADHD and bipolar disorder [91,92]. One polymorphism, V382A, exhibits decreased cell surface expression and transport capacity as well as uncoupled inactivation and trafficking [93,94]. Similarly, I425V, a SNP of the human serotonin transporter gene (SLC6A4), exhibits higher rates of transport [95] and has been found in two families with a high incidence of psychiatric disorders, including obsessive-compulsive disorder and Asperger's syndrome [96]. Approximately 20 SNPs of the human norepinephrine transporter gene (SLC6A2) have been reported [88]. The first disease-associated SLC6 protein variant, A457P, has no transport activity, decreased cell surface expression, and is associated with orthostatic intolerance [97,98]. A novel norepinephrine transporter variant has been identified in an ADHD patient that also exhibits orthostatic intolerance, suggesting that this phenotype may be indicative of norepinephrine transporter dysfunction that has implications for neuropsychiatric disorders [88]. A recent study in Caucasians suggested that an SNP in the VMAT1 gene was significantly associated with schizophrenia [99], but these results were not replicated in a similar study with Japanese schizophrenic subjects [100].

5. Neuropharmacology related to psychostimulant abuse

The primary mechanism for inactivation of monoamine signaling is transporter-mediated uptake of released monoamine neurotransmitters. Psychostimulants enhance monoamine signaling by interfering with transporter function (Fig. 1). However, psychostimulants differ in their relative affinity for dopamine, serotonin and norepinephrine transporters. For example, cocaine has approximately equal affinity

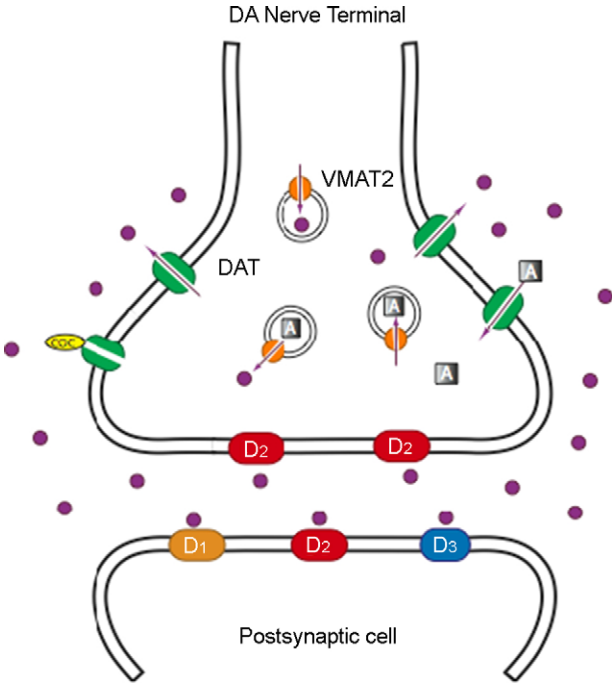

Fig. 1 – A representative dopaminergic synapse, including the pre- and post-synaptic terminals. Dopamine is packaged into vesicles in the presynaptic neuron via VMAT2. Once dopamine is released into the synapse, this neurotransmitter can bind to postsynaptic dopamine receptors, including the D_1, D_2, and D_3 dopamine receptors. Dopamine D_2 receptors are also localized at the presynaptic terminal, acting as a feedback mechanism to regulate dopamine release. The dopamine transporter is located perisynaptically and functions to terminate the actions of dopamine via a transport mechanism. Psychostimulants act at the DAT to alter normal dopamine receptor functions. Cocaine blocks the dopamine transporter, inhibiting uptake of dopamine into the presynaptic nerve terminal, thereby prolonging its effects in the synapse. Amphetamine also blocks the dopamine transporter and inhibits dopamine uptake, but also acts to release dopamine from intracellular vesicles. Abbreviations: A, amphetamine; COC, cocaine; DAT, dopamine transporter; VMAT2, vesicular monoamine transporter 2.

Table 2 – Drug affinities at monoamine transporters

Drug	Dopamine	Serotonin	Norepinephrine
(−) Cocaine	478[a]	304[a]	779[b]
(+) Amphetamine	34[b]	3830[b]	39[b]
(+) Methamphetamine	114[c]	2137[c]	48[c]
(±) Methylphenidate	82[d]	7600[d]	440[d]

[a] IC_{50} (nM): Matecka et al. (1996), J Med Chem 39:4704–16.
[b] Ki (nM): Rothman et al. (2001), Synapse 39:32–41.
[c] Ki (nM): Rothman et al. (2000), Synapse 35:222–7.
[d] IC_{50} (nM): Pan et al. (1994), Eur J Pharmacol 264:177–82.

for these three transporters (Table 2). In contrast, amphetamine, methamphetamine and methylphenidate all have relatively lower affinity for serotonin transporters compared to their affinity for dopamine and norepinephrine transporters. It is important to note, however, that there are significant discrepancies in studies reporting the potencies of psychostimulant drugs at monoamine transporters, ostensibly due to differences in experimental protocols, expression systems and tissue preparations [101]. In addition, psychostimulants differ in their actions as reuptake inhibitors versus substrate-type releasers [102,103]. Reuptake inhibitors bind to transporter proteins and interfere with transporter function but are not transported into the nerve terminal. Cocaine is an example of a reuptake inhibitor. In contrast, substrate-type releasers bind to transporter proteins and are subsequently transported into the cytoplasm of the nerve terminal. Releasers elevate extracellular monoamine levels by reversing the process of transporter-mediated exchange, thereby enhancing monoamine efflux. They also increase cytoplasmic levels of monoamines by interfering with vesicular storage [104,105]. Amphetamine and methamphetamine are examples of substrate-type releasers. Typically, releasers are more effective than reuptake inhibitors in increasing extracellular monoamines because the former increase the pool of neurotransmitters available for release by transporter-mediated exchange. Moreover, the effectiveness of releasers in increasing extracellular monoamines is not dependent upon the basal rate of neurotransmitter release. In contrast, the effectiveness of reuptake inhibitors is impulse-dependent and, therefore, limited by the tone of presynaptic activity.

In vivo studies have demonstrated that psychostimulants can interact with multiple monoamine transporters. However, the behavioral effects of psychostimulants associated with their addictive properties have been linked most closely to enhanced dopaminergic activity. The mesocorticolimbic dopamine system comprises dopamine neurons originating in the VTA of the midbrain that project to several limbic and cortical structures, including the nucleus accumbens, amygdala and prefrontal cortex [106,107]. Drug-induced increases in extracellular dopamine in the mesocorticolimbic dopamine system are critical in mediating the behavioral effects of psychostimulants. Two families of dopamine receptors termed D_1-like (D_1 and D_5 receptors) and D_2-like (D_2, D_3, and D_4 receptors) have been described [108,109], and both have been implicated in the abuse-related effects of cocaine [110–112]. Evidence to support this conclusion is derived from a variety of behavioral studies characterizing the acute effects of direct-acting dopamine agonists, dopamine uptake inhibitors and dopamine antagonists administered alone or in combination with cocaine and related psychostimulants.

Operant-conditioning procedures have been used effectively to characterize drug effects on behavior, including schedule-controlled behavior (model of stimulant effects), drug self-administration (model of reinforcing effects), reinstatement (model of relapse) and drug discrimination (model of subjective effects). In all cases, the behavioral effects of a drug are examined by establishing experimental control over a specific behavior and measuring changes from control performance following drug administration. Based on the principles of operant conditioning, presentation of a stimulus as a consequence of behavior may either increase or decrease the probability that a behavior will occur again. If a stimulus (e.g. food) increases the probability that a behavior will recur, then that stimulus is defined as a positive reinforcer. Reinforcement can be scheduled to occur intermittently based on well-defined rules, and there are a variety of intermittent schedules of reinforcement that have been used to characterize the behavioral effects of psychostimulants. Also important to the study of drug effects on behavior is the understanding that drugs can function as reinforcers to control behavior. Stimuli such as food and water can function as positive reinforcers, and extensive data from drug self-administration document that drugs can also function as positive reinforcers under a wide range of conditions. Drug self-administration procedures have been used extensively to characterize the abuse liability of psychostimulants. In reinstatement procedures, drug self-administration is extinguished by no longer reinforcing the behavior. Subsequently, a priming stimulus is presented non-contingent on the subject's behavior in order to reinstate previously extinguished self-administration. Non-contingent drug administration, drug-paired environmental stimuli, or environmental stressors can all induce reinstatement similar to relapse observed in humans. Lastly, in drug discrimination procedures, subjects are trained to respond differently based on the interoceptive cues associated with the administration of a drug. For example, one response is reinforced in the presence of one drug condition while another response is reinforced in the absence of a drug or in the presence of a different drug condition. Hence, the procedure is used to model the subjective or interoceptive effects of drugs.

In a series of comprehensive studies, a significant correlation was obtained between dopamine transporter binding potency *in vitro* and the locomotor-stimulant effects of cocaine analogs [113,114]. In addition, the inhibition constants of 19 different dopamine transporter inhibitors were highly and

positively correlated with their discriminative-stimulus effects in rodents trained to discriminate cocaine from saline [115]. Similarly, a high correlation was found between the ability of cocaine analogs to displace [^{3}H]cocaine in the caudate and the ability of those compounds to produce cocaine-like behavioral effects in squirrel monkeys [116–118]. Cocaine and selective dopamine uptake inhibitors exert similar effects on schedule-controlled behavior and are reliably self-administered in monkeys [116,119–122]. Moreover, some direct-acting dopamine agonists maintain self-administration in rodents [123] and monkeys [124,125]. Lastly, dopamine antagonists can attenuate specific behavioral effects of cocaine including its reinforcing effects [126], its discriminative-stimulus effects [127–129] and its stimulant effects on schedule-controlled behavior [119,130–132]. The results obtained in behavioral studies provide compelling evidence that dopamine plays a major role in the neuropharmacology of cocaine.

The relevance of the dopamine transporter in the reinforcing effects of cocaine is supported further by human and nonhuman primate neuroimaging studies. In human cocaine users, a significant correlation was observed between dopamine transporter occupancy and the subjective high reported following administration of cocaine [133] or the behavioral stimulant, methylphenidate [134]. Doses of cocaine within the range used by humans resulted in dopamine transporter occupancy between 67% and 69% in baboons [135]. Moreover, doses of cocaine that maintained peak response rates in drug self-administration studies resulted in dopamine transporter occupancy between 65% and 76% in rhesus monkeys [136,137]. In addition, dopamine transporter occupancy has been determined for dopamine transporter inhibitors shown to be effective in reducing cocaine self-administration. Doses of GBR 12909 that decreased cocaine self-administration in rhesus monkeys resulted in dopamine transporter occupancy greater than 50% in baboons [138] and rhesus monkeys [137]. Similarly, doses of phenyltropane derivatives of cocaine with selectivity for the dopamine transporter decreased cocaine self-administration in rhesus monkeys at dopamine transporter occupancies between 72% and 84% [136,137]. Collectively, these results indicate that dopamine transporter occupancy is an important determinant of the reinforcing effects of cocaine and of the effectiveness of dopamine transporter inhibitors to reduce cocaine self-administration.

The dopaminergic system is clearly an important site of action for psychostimulants, but preclinical studies have indicated that the serotonergic system can effectively modulate the behavioral effects of cocaine and amphetamine. Although compounds that selectively increase serotonin neurotransmission lack behavioral-stimulant effects and do not reliably maintain self-administration behavior [139,140], a negative relationship was observed between the potencies of several cocaine- and amphetamine-like drugs in self-administration studies and their binding affinities for serotonin uptake sites [141,142]. Co-administration of agents that induce robust increases in both dopamine and serotonin produces minimal behavioral-stimulant effects [143] and does not maintain self-administration behavior [144] in rodents. Similarly, monoamine-releasing agents have decreased reinforcing efficacy in rhesus monkeys when serotonin-releasing potency is increased relative to dopamine [145]. The behavioral and neurochemical profile of dopamine transporter inhibitors is also influenced by their actions at multiple monoamine transporters in squirrel monkeys [146]. Consistent with these results, administration of the serotonin uptake inhibitor fluoxetine decreased self-administration of cocaine [147] and amphetamine [148] in rodents, and self-administration of cocaine in rhesus monkeys [149]. In nonhuman primate studies, the serotonin uptake inhibitors citalopram, fluoxetine and alaproclate attenuated the behavioral-stimulant effects of cocaine on schedule-controlled behavior [140,150]. The serotonin direct agonist, quipazine, also attenuated the behavioral-stimulant effects of cocaine, whereas the serotonin antagonists, ritanserin and ketanserin, enhanced the behavioral-stimulant effects of cocaine [140]. Lastly, the serotonin uptake inhibitor alaproclate attenuated cocaine self-administration and cocaine-induced increases in extracellular dopamine in squirrel monkeys [151] and cocaine-induced activation of prefrontal activity in rhesus monkeys [152]. Co-administration of fluoxetine or citalopram in combination with the highly selective dopamine transporter inhibitor, RTI-336, significantly enhanced the effectiveness of RTI-336 to suppress cocaine self-administration in rhesus monkeys [153]. Collectively, there is a growing body of evidence to suggest that increasing brain serotonin activity can attenuate the behavioral-stimulant and reinforcing effects of psychostimulants.

Brain serotonin systems are ideally situated to modulate the activity of dopamine neurons and the behavioral effects of dopamine uptake inhibitors such as cocaine. Serotonin neurons from the dorsal and median raphe nuclei innervate the dopaminergic cell bodies and terminal regions of the nigrostriatal and mesolimbic dopamine systems, and the convergence of serotonin terminals and dopamine neurons has been visualized in the VTA and nucleus accumbens at the light and electron microscopic levels [154,155]. Serotonin can act on cell bodies to decrease the firing rate of dopamine neurons or at terminals to decrease dopamine release. In either case, the ability of serotonin to attenuate the behavioral effects of cocaine may result from an attenuation of cocaine-induced elevation of extracellular dopamine. Alternatively, serotonin may act postsynaptically to dopamine neurons, attenuating the effects of cocaine-induced increases of extracellular dopamine on a downstream component of the pathway.

There is a growing consensus that stimulation of serotonin $5HT_{2C}$ receptors inhibits the function of the mesolimbic dopamine system [156]. Firing rates of dopamine neurons in the VTA are decreased by serotonin uptake inhibitors [157] and selective serotonin $5HT_{2C}$ agonists [158], resulting in a decrease in nucleus accumbens dopamine levels [159]. Conversely, selective serotonin $5HT_{2C}$ antagonists increase the activity of these neurons [160], leading to increased dopamine release in the nucleus accumbens [161]. Since serotonin $5HT_{2c}$ receptors appear to be located exclusively on GABA neurons [162], the effects of serotonin $5HT_{2C}$ receptor stimulation are likely to be indirectly mediated by an enhancement of GABA-mediated inhibition of VTA dopamine neurons. Localization of serotonin $5HT_{2C}$ receptors on GABAergic terminals may also explain the conflicting results, which have been obtained in previous electrophysiological, neurochemical and behavioral studies. Some studies investigating interactions between serotonin and dopamine have

concluded that serotonin can exert an excitatory influence on dopamine activity [163] and release [164,165]. Stimulation of serotonin $5HT_{1B}$ receptors can enhance cocaine reinforcement [166], likely by decreasing GABA-mediated inhibition in the VTA [163]. Serotonin $5HT_3$ receptors also appear to play a facilitatory role in the behavioral effects of dopamine agonists [167,168]. These seemingly disparate results likely reflect the complexity of interactions between serotonin and dopamine systems, and the serotonin receptor subtypes influenced by drug administration.

The norepinephrine system has considerable anatomical and functional connectivity to the mesolimbic dopamine system. There is significant noradrenergic innervation of the shell subregion of the nucleus accumbens [169,170]. The locus coeruleus, the primary norepinephrine nucleus in the brain, projects directly to the VTA and influences neuronal firing of dopamine neurons [171]. Stimulation of the locus coeruleus can increase the activity of VTA dopamine neurons; and this effect is blocked by an α_1-adrenoreceptor antagonist [172]. In addition, lesions of the locus coeruleus can decrease basal release of dopamine in the nucleus accumbens [173]. It appears that interactions between norepinephrine and dopamine may play an important role in the behavioral pharmacology of psychostimulants. For example, amphetamine-induced release of dopamine in the nucleus accumbens and conditioned place preference to amphetamine are attenuated following depletion of norepinephrine in the prefrontal cortex of rodents [174]. Lesion of the locus coeruleus or inactivation of α_1 adrenoreceptors can also attenuate amphetamine- and cocaine-induced locomotion and sensitization in rodents [175–177]. Similarly, α_2-adrenoreceptor agonists which decrease norepinephrine release via autoreceptor activation block stress-induced reinstatement of extinguished cocaine self-administration behavior in rodents [178]. Studies in nonhuman primates also support a role for norepinephrine uptake and α_1-adrenoreceptor mechanisms in the discriminative-stimulus effects of cocaine [179]. Moreover, the α_2-adrenoreceptor antagonist, yohimbine, can reinstate cocaine-seeking behavior in squirrel monkeys [180]. More recent studies in squirrel monkeys have also documented that norepinephrine transporter inhibition can play a significant role in cocaine-induced reinstatement [181]. There is also a significant positive correlation between potency of drug-induced norepinephrine release and the drug dose that produces stimulant-like subjective effects in humans following oral administration [182]. However, it should be noted that there is little evidence that norepinephrine plays a primary role in the reinforcing properties of psychomotor stimulants in rodents [183] or nonhuman primates [140,184–186].

The interaction between glutamatergic and dopaminergic systems has been an area of increasing interest in drug abuse and mental health research. Anatomical substrates for glutamate-dopamine interactions have been well characterized in rodents [187]. Dopaminergic afferents from the VTA to the dorsal striatum, nucleus accumbens and prefrontal cortex are positioned to modulate glutamate function. Conversely, the VTA, dorsal striatum and nucleus accumbens receive significant glutamatergic innervation from a variety of brain regions including the prefrontal cortex, hippocampus, basolateral amygdala and thalamus. Importantly, a substantial literature derived from rodent studies has documented that glutamate receptor function plays a major role in the behavioral pharmacology of cocaine and other psychomotor stimulants. In particular, glutamatergic systems have been implicated in the development of locomotor sensitization, conditioned place preference, drug self-administration and reinstatement of extinguished drug self-administration behavior [188–192]. Recent evidence indicates that metabotropic glutamate receptors (mGluRs) play an important role in the behavioral effects of cocaine associated with its abuse liability. Administration of an mGluR2/3 agonist decreased dopamine and glutamate release in the nucleus accumbens, striatum and prefrontal cortex [193–196], suggesting that glutamatergic tone on mGluR2/3 suppresses extracellular levels of dopamine and glutamate. The primary origin of extrasynaptic glutamate appears to be nonvesicular glutamate regulated by cystine/glutamate transporters [196,197]. Withdrawal from repeated exposure to cocaine in rodents led to reduced levels of extracellular glutamate in the nucleus accumbens due to reductions in cystine/glutamate exchange [198,199]. Restoration of cystine/glutamate exchange by systemically administered *N*-acetylcysteine (NAC) normalized glutamate levels in cocaine-treated rats, and prevented cocaine-induced reinstatement. Overall, a growing body of evidence derived from rodent studies indicates that glutamate plays a fundamental role in the maintenance and reinstatement of stimulant self-administration behavior [200–202]. Lastly the mGluR5 subtype has also been implicated in cocaine self-administration. mGluR5-deficient mice did not acquire intravenous self-administration of cocaine (105), and pretreatment with the mGluR5 antagonist, MPEP, suppressed cocaine self-administration in squirrel monkeys [203].

The inhibitory amino acid, GABA, is widely distributed in the central nervous system and can modulate basal dopamine and glutamate release [204]. The VTA contains GABAergic inhibitory interneurons that function to control the firing rate of VTA dopamine neurons [205–207]. Moreover, the majority of projection neurons in the nucleus accumbens are GABAergic neurons, some of which project to the VTA and regulate the activity of dopamine neurons [208]. Several studies have indicated that GABAergic compounds can reliably modulate the neurochemical and behavioral effects of cocaine [209,210]. Allosteric $GABA_A$ agonists, such as benzodiazepines and barbiturates, can inhibit dopamine and glutamate activity but have prominent sedative and hypnotic effects. However, there is considerable interest in $GABA_B$ agents, such as baclofen, due to their attenuation of glutamate and dopamine release [204,211,212] and their suppression of cocaine self-administration behavior across a wide range of schedules of reinforcement and access conditions [210,213–215]. In addition, pharmacological inhibition of GABA-transaminase, the major enzyme involved in the metabolism of GABA, can lead to a rapid increase in extracellular GABA and a corresponding attenuation of cocaine self-administration behavior at doses that do not influence locomotor activity [216,217]. Inhibition of GABA-transaminase activity with gamma-vinyl GABA can also block cocaine-induced lowering of brain stimulation reward thresholds [218]. Although psychostimulants do not have direct pharmacological effects on GABAergic systems, there

is convincing evidence that GABA can modulate the neurochemical and behavioral effects of psychostimulants.

6. Neurobiology of chronic psychostimulant administration

Repeated exposure to psychostimulants can lead to robust and enduring changes in neurobiological substrates and corresponding changes in sensitivity to acute drug effects on neurochemistry and behavior. Diminished sensitivity to the effects of a drug during repeated exposure is indicative of tolerance, whereas enhanced sensitivity is indicative of sensitization. Both tolerance and sensitization have been reported to develop during repeated administration of stimulants in animal studies [219]. However, the outcome depends upon a variety of procedural variables including the drug effect under investigation, the dosing regimen, the environmental context associated with drug administration and the animal species. The vast majority of studies have focused on sensitization to locomotor-stimulant effects in rodent models. Stimulants including cocaine and amphetamines can produce robust sensitization in rodents, usually identified as a progressive increase in locomotor activity or stereotyped behavior with drug dosing [220]. In fact, sensitization has been proposed as a general model of neural plasticity whereby drug-induced changes in behavior can be linked to concomitant changes in molecular mechanisms.

There is substantial evidence that the mesocorticolimbic dopamine system and its excitatory glutamatergic inputs are critical for the development of sensitization to the behavioral effects of psychostimulants [191,221]. Studies involving microinjection of drugs into discrete brain regions have indicated that the VTA, a region rich in dopamine cell bodies, plays a critical role in the development of sensitization. In contrast, the nucleus accumbens, a major dopamine projection area from the VTA, appears to be more closely linked to the expression of sensitization. For example, microinjections of dopamine D_1-receptor antagonists [222,223] or glutamate N-methyl-D-aspartate (NMDA) receptor antagonist [224] into the VTA can disrupt the development of sensitization. However, glutamate NMDA antagonists do not bock the expression of sensitization [225]. Similarly, dopamine antagonists can block the development of sensitization to psychostimulants without blocking its expression [226]. Glutamatergic afferents from the prefrontal cortex to the VTA and the nucleus accumbens have been implicated in both the development and expression of sensitization to cocaine and amphetamine [227]. Sensitized animals also reliably show an augmented response to drug-induced increases in extracellular glutamate and dopamine in the nucleus accumbens [188,228]. Collectively, there is convincing evidence to suggest that glutamatergic afferents from the prefrontal cortex produce adaptations in the VTA that mediate the development of sensitization to psychostimulants, and that secondary adaptations within the nucleus accumbens are necessary for the expression of sensitization.

Sensitization to psychostimulants has been demonstrated in nonhuman primates, but studies to demonstrate sensitization in humans have yielded equivocal results. Rhesus monkeys trained to self-administer cocaine showed an augmented response to cocaine-induced elevations in striatal extracellular dopamine that emerged over a 2-year period of drug exposure [229]. Chronic amphetamine exposure in nonhuman primates also induced a pattern of behavioral response that resembled the positive-like symptoms of schizophrenia [230]. Negative-like symptoms have also been observed in nonhuman primates following chronic amphetamine treatment [231]. More recently, a longitudinal study in rhesus monkeys exposed to repeated, escalating doses of amphetamine documented enhanced behavioral responses to subsequent acute low-dose amphetamine challenges [232]. Moreover, the enhanced behavioral responses to amphetamine challenge were evident up to 28 months post-withdrawal from chronic treatment. Several human studies in normal volunteers with no history of prior stimulant use reported evidence of sensitization to psychological (energy level and mood) and physiological (eye-blink rates) measures following two or three daily doses of amphetamine [233–235]. The outcome measures demonstrated enhanced increases following the last amphetamine dose compared to the first dose, suggesting that behavioral sensitization can be documented in human subjects. However, studies conducted in experienced stimulant users have not found evidence of sensitization. Experienced cocaine users failed to show sensitization after one or four prior cocaine exposures [236,237]. Similarly, subjects with histories of stimulant use failed to show sensitization to oral amphetamine or methamphetamine [238,239]. Repeated amphetamine challenges in patients with first-episode manic or schizophrenic psychosis also failed to induce sensitization [240].

There is legitimate concern that stimulant treatment during adolescence could have significant and enduring effects on reward processes relevant to mood regulation and risk for drug abuse. Preclinical studies have clearly documented that stimulants can have profound and long-lasting behavioral and neurobiological effects [191,241]. Repeated exposure to stimulants in rodents reliably produces sensitization to their locomotor-stimulant effects [242,243] and can induce cross-sensitization with different classes of stimulant drugs [244]. Locomotor sensitization has been reported for low-dose stimulant administration intended to model therapeutic dosing [243]. Importantly, repeated dosing protocols that produce locomotor sensitization in rats can enhance the reinforcing properties of stimulants [245–248]. Once established, these behavioral and associated neurobiological changes can be remarkably stable and enduring [191,249,250]. Collectively, the results of laboratory studies in rodents raise significant concerns that prior exposure to stimulants, including those prescribed for the treatment of ADHD, may increase vulnerability to drug abuse in humans [251]. However, this area of investigation has received inadequate attention in human subjects, and has not been approached with the experimental control and rigor afforded in animal studies. While ADHD is prevalent in treatment-seeking substance abusers [252], clinical studies have not provided direct support for concerns that have emerged from preclinical studies. On the contrary, recent reports suggest the possibility of reduced risk for substance disorders in children with ADHD who received therapeutic administration of stimulants such as methylphenidate [253,254]. There is an

obvious need to develop clinically relevant animal models that effectively extrapolate to the human condition, and to establish a better understanding of how chronic drug exposure in adolescents alters the neuropharmacology of monoamine systems.

Efforts to define the long-term neurobiological consequences of psychostimulant administration have focused primarily on the dopaminergic system in adult subjects and have yielded inconsistent results. For example, cocaine exposure has been reported to increase, decrease or have no effect on dopamine transporter density in rodents [255–261]. Similarly, chronic cocaine administration in rodents has been reported to increase, decrease or have no effect on dopamine D_1- or D_2-receptor density [262–265]. Recent studies indicate that repeated cocaine use alters the intracellular cAMP signaling pathway in the nucleus accumbens, disrupting the interactions between D_1 and D_2 dopamine receptors [266]. The equivocal results likely reflect different dosing regimens and withdrawal periods, as well as the use of noncontingent drug administration protocols that do not model voluntary drug use. Active drug self-administration protocols and periods of drug abstinence can have profound influences on neuroadaptive changes in dopamine systems [267]. Accordingly, a more consistent picture has emerged from nonhuman primate studies of cocaine self-administration. For example, in rhesus monkeys trained to self-administer cocaine intravenously for 5 days, 3.3 months, or 1.5 years, initial exposure lead to moderate decreases in dopamine transporter density in the striatum as determined postmortem with quantitative autoradiography [268]. However, longer exposure resulted in increased striatal dopamine transporter density that was most pronounced in the ventral striatum at the level of the nucleus accumbens. Importantly, the increases in dopamine transporter binding observed after long-term cocaine self-administration in nonhuman primates corresponded closely to increases observed in post-mortem tissue of human cocaine addicts [269,270]. In related studies, rhesus monkeys trained to self-administer cocaine on a daily basis over 18–22 months showed lower dopamine D_1 binding density as determined post-mortem with quantitative autoradiography [271,272]. The effects were most pronounced in regions of the striatum where the nucleus accumbens is most fully developed. In parallel studies using the same dosing schedule and quantitative autoradiography, dopamine D_2 binding density was lower in all regions of the striatum rostral to the anterior commissure [272,273]. In a recent PET neuroimaging study in rhesus monkeys, D_2-receptor availability decreased by 15–20% within one week of initiating cocaine self-administration and remained reduced by approximately 20% during one year of exposure [274]. Collectively, these drug-induced changes in the status of the dopamine system may contribute to the development of dependence associated with long-term psychostimulant use.

Functional neuroimaging techniques have been used effectively in humans to characterize the long-term consequences of stimulant exposure in the context of drug abuse. Compared to controls, detoxified cocaine abusers had a marked decrease in dopamine release as measured by methylphenidate-induced decreases in striatal [^{11}C]raclopride binding [133], and cocaine-dependent subjects showed a blunted response to amphetamine-induced dopamine release [275]. The self-reports of ''high'' induced by methylphenidate were also less intense in cocaine abusers. The decrease in dopamine release in the striatum has been hypothesized to underlie the decrease in sensitivity to natural reinforcers in drug abusers [276,277]. The density of the dopamine transporter and receptors in humans has also been evaluated with positron emission tomography (PET) imaging studies. In cocaine abusers, dopamine transporter density appears to be elevated shortly after cocaine abstinence but then to normalize with long-term detoxification [278]. In contrast, PET studies characterizing dopamine D_2 receptors have reliably documented long-lasting decreases in D_2-receptor density in stimulant abusers [279]. The reduction in D_2-receptor function coupled with dysfunctional dopamine release may further decrease sensitivity of reward circuits to stimulation by natural rewards and increase the risk for drug-taking [280]. Lastly, regional brain glucose metabolism measured by 2-fluoro-2-deoxy-D-glucose (FDG) uptake has been characterized in conjunction with dopamine D_2 receptors [281,282]. Reductions in striatal D_2 receptors were associated with decreased metabolic activity in the orbital frontal cortex and anterior cingulate cortex in detoxified individuals. In contrast, the orbital frontal cortex was hypermetabolic in active cocaine abusers [283]. Collectively, these findings observed in stimulant abusers document significant dysregulation of dopamine systems that are reflected in brain metabolic changes in areas involved in reward circuitry. Unfortunately, such well-designed clinical studies have not been conducted in the context of stimulant use for therapeutic purposes. However, therapeutic doses of methylphenidate block dopamine transporter function and increase extracellular dopamine [284,285]. There is also a positive correlation between clinical improvement and reduction in dopamine transporter density in the basal ganglia following methylphenidate treatment [286]. Functional magnetic resonance imaging studies suggest that methylphenidate increases frontal cortical activity in children with ADHD [287], while PET imaging studies suggest that methylphenidate modulates brain regions associated with motor function in adults with ADHD [288]. Earlier PET studies using FDG in adults with ADHD found more limited brain metabolic effects following acute administration of d-amphetamine [289] and following chronic administration of d-amphetamine or methylphenidate [290]. Clearly, there is a need to conduct well-controlled laboratory studies to document the long-term consequences of low-dose stimulant exposure on dopaminergic function and brain metabolism.

Although significant attention has been focused on the dysregulation of the dopaminergic system, it should be emphasized that chronic exposure to stimulants can have long-term neurobiological effects on numerous neurotransmitter systems. Notably, long-term alterations in the serotonin system have also been reported [291–293]. Chronic exposure to cocaine enhanced sensitivity of 5-HT_{1A} receptors to inhibit GABAergic medium spiny neurons of the striatum [294] and reduced serotonin concentrations in the frontal cortex [295] in rats. However, a post-mortem study of human cocaine users documented higher serotonin levels in the frontal cortex compared to matched controls [296]. A recent study in rhesus monkeys showed an increase in serotonin

transporters in the caudate nucleus and putamen following a history of cocaine self-administration [297]. Dysregulation of the noradrenergic systems may also be associated with chronic cocaine exposure. Altered noradrenergic tone was observed during cocaine withdrawal in human cocaine abusers [298], and chronic cocaine self-administration in nonhuman primates upregulated the norepinephrine transporter and decreased cerebral metabolism in the bed nucleus stria terminalis, a brain region that plays a key role in cocaine withdrawal and stress-induced reinstatement of extinguished self-administration behavior [299]. Postmortem studies showed that chronic exposure to cocaine upregulated NET protein expression and [^{3}H]nisoxetine binding sites in the insular cortex in cocaine addicts [300]. Finally, enduring changes in glutamatergic function have been associated with repeated administration of psychostimulants. For example, basal extracellular levels of glutamate in the nucleus accumbens are decreased in rats with a history of repeated cocaine exposure [188] and there is a corresponding augmentation of cocaine-induced increases in glutamate [188,301]. Others have reported a reduction in signaling through group I and group II metabotropic glutamate receptors [199,302] and a reduction in sensitivity of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) glutamate receptors to electrical stimulation of the prefrontal cortex [303]. An enhanced inhibitory effect of dopamine on excitatory AMPA currents has also been reported [304]. The apparent downregulation of presynaptic and postsynaptic glutamate transmission following repeated cocaine exposure has been linked to cocaine-induced reinstatement of extinguished self-administration behavior, and may have direct relevance toward understanding relapse to stimulant use in humans [197,202].

7. Medications development for psychostimulant abuse

There is a growing appreciation that drug addiction is a chronic relapsing disorder with a biological basis. Significant advances in the understanding of neurobiological mechanisms underlying drug abuse and dependence have guided pharmacological treatment strategies to improve clinical outcome. Considerable effort has been directed toward the development of effective medications for substance abuse disorders and has lead to useful pharmacological interventions. Notably, methadone has been an effective medication and adjunct in the treatment of heroin abuse for many years [305,306], nicotine replacement has been effective in smoking cessation [307], and naltrexone has documented efficacy in the treatment of alcoholism [308,309]. During the past two decades, psychostimulant addiction has been a major focus of multidisciplinary research efforts, including molecular approaches, preclinical behavioral studies and clinical trials. However, no suitable medication has been approved for the treatment of stimulant use disorders [310,311]. It should be noted that the vast majority of clinical research has focused on cocaine rather than other psychostimulants such as amphetamines and methylphenidate. The extent to which outcomes related to cocaine addiction can be extended to other psychostimulants remains unclear [312]. There are multiple pharmacological approaches in the treatment of cocaine abuse and dependence, including: (1) functional-antagonists treatments which block the euphoric effects of cocaine and extinguish illicit drug use; (2) functional-agonists treatments which replace some of the pharmacological effects of cocaine, thereby stabilizing neurochemistry and behavior; and (3) treatments that attenuate symptoms of cocaine toxicity or withdrawal [310,312]. Numerous medications have been evaluated for treatment of cocaine dependence that include a wide range of pharmacological targets. Reviews of the clinical literature have reported no significant benefit from antidepressants or dopamine agonists for cocaine dependence [313,314]. Antagonists strategies designed to block the euphoric or positive effects of psychostimulants with antipsychotic medications have included risperidone [315], flupenthixol [316] and olanzapine [317] and have yielded negative clinical outcome largely due to poor compliance and treatment retention. Several novel approaches that have shown some clinical promise include disulfiram, a well-established medication for treatment of alcoholism [318–320], and $GABA_B$ receptor agonists [210]. A recent review also reported promising results for agonist-like stimulant medications in the treatment of cocaine and amphetamine dependence [310].

Tricyclic antidepressants are the best-characterized class of medications for the treatment of cocaine dependence. Desipramine was the first medication reported to be effective in an outpatient, controlled clinical trial. An initial meta-analysis found desipramine to be effective in reducing relapse to cocaine use [321], but subsequent clinical trials did not confirm its effectiveness [322,323] or found it effective only for limited periods [324]. Based on pharmacological mechanisms, there is no convincing rationale for selecting desipramine over other tricyclic antidepressants [312]. Initial human laboratory studies with the selective serotonin reuptake inhibitor, fluoxetine, were encouraging. A 4-week inpatient study in healthy volunteers found that fluoxetine significantly decreased subjective ratings of cocaine-induced positive mood effects [325]. However, controlled clinical trials with fluoxetine have not documented significant advantages over placebo [326,327]. Similarly, clinical effectiveness has not been documented for the antidepressants bupropion [328] or nefazodone [329].

Agonist medications share pharmacological mechanisms of action with the abused drug, thereby producing some common neurochemical effects. Agonist medications for treatment of cocaine dependence have included direct dopamine receptor agonists and indirect dopamine receptor agonists. Preclinical studies in nonhuman primates involving chronic treatment with direct dopamine receptor agonists on cocaine self-administration have not yielded encouraging results. For example, chronic treatments with full and partial dopamine D_1-receptor agonists produced nonselective decreases in cocaine- and food-maintained responding in squirrel monkeys [330] or moderately selective decreases in cocaine-maintained responding in rhesus monkeys [331]. The D_2/D_3-receptor agonist, quinpirole, failed to reliably suppress cocaine self-administration at doses that produced overt toxicity in squirrel monkeys [332]. Clinical studies with dopamine receptor agonists have also been disappointing. For example, bromocriptine is a D_2-like receptor agonists and a partial D_1-like receptor agonist used mainly in the treatment

of Parkinson's disease. In a human laboratory study, pretreatment with bromocriptine prior to cocaine administration had no effect on cocaine-induced euphoria [333]. Moreover, the results of outpatient clinical trials with bromocriptine were inconclusive [312]. A recent 8-week open label study with combined bupropion and bromocriptine in cocaine-dependent subjects did not find improvement based on cocaine-positive urine screens [334]. Collectively, these findings do not support the use of bromocriptine as a pharmacotherapy for cocaine dependence.

Studies evaluating the effects of indirect dopamine agonists have yielded mixed but more encouraging results. Mazindol, a dopamine and norepinephrine reuptake inhibitor used in the treatment of obesity, did not alter the subjective effects of cocaine in a human laboratory study [335]. Moreover, in a 6-week, placebo-controlled study in cocaine dependent subjects, mazindol did not differ from placebo in reducing cocaine use and mazindol treatment was not well tolerated [336]. Methylphenidate, a dopamine and norepinephrine reuptake inhibitor used in the treatment of ADHD and narcolepsy, was well tolerated and led to better retention than placebo, but was not effective in reducing cocaine use in cocaine dependent subjects [337]. In a separate study in cocaine dependent subjects with ADHD, there was no significant reduction in cocaine use [338]. However, clinical studies with the indirect dopamine agonist, disulfiram, have been more encouraging. Disulfiram blocks the conversion of dopamine to norepinephrine by inhibiting the enzyme dopamine β-hydroxylase, thereby increasing brain dopamine concentrations. Two controlled clinical trials in cocaine addicts that were not alcoholics found disulfiram to be significantly better than placebo in promoting cocaine abstinence [318,319]. A recent outpatient study in cocaine dependent subjects replicated these earlier findings, showing that disulfiram was more effective than placebo in reducing cocaine use [320]. Collectively, the results suggest that disulfiram may be effective in treating cocaine addicts, including those who are not alcoholic.

There is growing support from preclinical studies in nonhuman primates and recent clinical studies for the use of stimulant medications in the treatment of cocaine dependence [310,339–342]. A number of studies in nonhuman primates provide evidence that dopamine transporter inhibitors can effectively attenuate cocaine self-administration [120,122,136,137,343]. Hence, the development of compounds that target the dopamine transporter represents a logical approach for the pharmacological treatment of cocaine dependence. Similarly, chronic treatment with the nonselective monoamine releaser, dextroamphetamine, produced sustained and selective decreases in cocaine self-administration in rhesus monkeys [340,341]. A possible limitation to the use of dopamine transport inhibitors and monoamine releasers as medications for treatment of cocaine dependence is their potential for abuse, given their documented reinforcing effects. However, recent evidence suggests that the reinforcing effectiveness of dopamine transporter inhibitors may be limited by dual actions at the dopamine and serotonin transporters. For example, a cocaine analog with high affinity at dopamine and serotonin transporters was not reliably self-administered when substituted for cocaine, yet suppressed cocaine self-administered at low levels of dopamine transporter occupancy [137]. Similarly, monoamine-releasing agents exhibited decreasing reinforcing efficacy when the serotonin-releasing potency was increased relative to the dopamine-releasing potency [145]. Accordingly, combined actions at dopamine and serotonin transporters may enhance effectiveness in reducing cocaine use, and limit the abuse liability of the medication [153]. Importantly, compelling data have emerged from clinical research supporting indirect agonist pharmacotherapy for stimulant abuse and dependence. Well-designed, placebo-controlled clinical trials in cocaine-dependent subjects found sustained-released dextroamphetamine better than placebo in reducing cocaine intake [310].

Medications that target glutamatergic function are reasonable candidates given the involvement of glutamatergic circuits in reward-related brain regions and evidence of cocaine-induced dysregulation of glutamate function [344]. Modafinil, approved for the treatment of narcolepsy, enhances glutamate function via unidentified mechanisms that induce increases in glutamate synthesis and striatal glutamate brain levels [345]. Interestingly, modafinil has clinical effects in nondependent subjects that are opposite to the cocaine-withdrawal syndrome [346]. In patients with severe cocaine withdrawal symptoms, modafinil treatment resulted in higher rates of cocaine abstinence and treatment retention. In a separate study, the subjective effects of cocaine administration in cocaine-dependent subjects were significantly reduced [347]. Modafinil was well tolerated in both studies and is currently being investigated for treatment of cocaine dependence in large, controlled clinical studies. Although a functional interaction between modafinil and the dopamine transporter has been questioned on the basis of its low affinity for the dopamine transporter [348], recent studies have documented modafinil-induced enhancement of dopamine function [349,350] that may account for the initial positive clinical outcomes in cocaine addicts [351].

Recently, the GABAergic system has received significant attention as a potential target for the pharmacological treatment of cocaine dependence [311]. For example, baclofen is an antispasticity agent that is a nonselective $GABA_B$ agonist. In a placebo-controlled study in cocaine dependent subjects, baclofen treatment enhanced cocaine abstinence compared to placebo [352]. Tiagabine is an antiepileptic medication that increases synaptic levels of GABA by inhibiting GABA transporters. A placebo-controlled pilot study in opioid-dependent patients maintained on methadone reported that tiagabine attenuated cocaine use [353]. Topiramate is another antiepileptic medication that potentiates GABAergic transmission, but it has a complex pharmacology that includes antagonism of AMPA/kainate glutamate receptors [354]. In a recent placebo-controlled pilot study in cocaine dependent subjects, topiramate treatment enhanced cocaine abstinence [355]. Collectively, these initial studies suggest that the GABAergic systems may be a useful pharmacological target for cocaine medications development, although additional, larger scale clinical trials are clearly warranted.

8. Summary

The abuse liability of psychostimulants is well established and represents a significant public health concern. Currently, no

effective pharmacotherapy for psychostimulant abuse has demonstrated efficacy for long-term use. A better understanding of the neuropharmacological effects of cocaine and related psychostimulants has supported efforts to develop and improve useful medications for psychostimulant abuse and dependence. An extensive literature documents the critical importance of the monoamines in the behavioral pharmacology and addictive properties of psychostimulants. In particular, dopamine plays a primary role in their reinforcing effects and abuse liability. The relevance of the dopamine transporter in the reinforcing effects of cocaine is supported by numerous preclinical studies of drug self-administration and, more recently, by nonhuman primate and human neuroimaging studies. Also, a growing literature indicates that the serotonergic and noradrenergic systems can effectively modulate the neurochemical and behavioral effects of cocaine and amphetamine. Similarly, cortical glutamatergic systems provide important regulation of dopamine function, and GABAergic systems provide inhibitory neuromodulation of monoaminergic and glutamatergic function. Repeated exposure to psychostimulants can lead to robust and enduring changes in all of these neurobiological substrates, resulting in altered sensitivity to acute drug effects on neurochemistry and behavior, as well as dysregulation of brain function linked to dependence and addiction. Recent approaches in medications development to treat psychostimulant abuse and dependence have focused largely on these well-established neurobiological mechanisms with some degree of success. In particular, functional agonist treatments may be used effectively to stabilize neurochemistry, influence behavior and lead to long-term abstinence. Similarly, medications that target glutamatergic and GABAergic function are reasonable candidates that have received significant attention, and some have demonstrated effectiveness in reducing cocaine use and enhancing cocaine abstinence. However, these encouraging results will require additional clinical studies in order to identify safe and efficacious pharmacotherapies.

REFERENCES

[1] Williams RJ, Goodale LA, Shay-Fiddler MA, Gloster SP, Chang SY. Methylphenidate and dextroamphetamine abuse in substance-abusing adolescents. Am J Addict 2004;13:381–9.

[2] Darvesh AS, Gudelsky GA. Evidence for a role of energy dysregulation in the MDMA-induced depletion of brain 5-HT. Brain Res 2005;1056:168–75.

[3] Ricaurte GA, McCann UD. Experimental studies on 3,4-methylenedioxymethamphetamine (MDA, ''ecstasy'') and its potential to damage brain serotonin neurons. Neurotox Res 2001;3:85–99.

[4] Xie T, Tong L, McLane MW, Hatzidimitriou G, Yuan J, McCann U, et al. Loss of serotonin transporter protein after MDMA and other ring-substituted amphetamines. Neuropsychopharmacology 2006;31:2639–51.

[5] Amara SG, Arriza JL. Neurotransmitter transporters: three distinct gene families. Curr Opin Neurobiol 1993;3:337–44.

[6] Gether U, Andersen PH, Larsson OM, Schousboe A. Neurotransmitter transporters: molecular function of important drug targets. Trends Pharmacol Sci 2006;27:375–83.

[7] Ravna AW. Three-dimensional models of neurotransmitter transporters and their interactions with cocaine and S-citalopram. World J Biol Psychiatry 2006;7:99–109.

[8] Kavanaugh MP. Neurotransmitter transport: models in flux. Proc Natl Acad Sci USA 1998;95:12737–8.

[9] Giros B, el Mestikawy S, Godinot N, Zheng K, Han H, Yang-Feng T, et al. Cloning, pharmacological characterization, and chromosome assignment of the human dopamine transporter. Mol Pharmacol 1992;42:383–90.

[10] Yamashita A, Singh SK, Kawate T, Jin Y, Gouaux E. Crystal structure of a bacterial homologue of Na^+/Cl-dependent neurotransmitter transporters. Nature 2005;437:215–23.

[11] Barker EL, Blakely RD. Norepinephrine and serotonin transporters. In: Bloom FE, Kupfer DJ, editors. Psychopharmacology: the fourth generation of progress. New York: Raven Press; 1995. p. 321–33.

[12] Giros B, Caron MG. Molecular characterization of the dopamine transporter. Trends Pharmacol Sci 1993;14:43–9.

[13] Sonders MS, Amara SG. Channels in transporters. Curr Opin Neurobiol 1996;6:294–302.

[14] Kimmel HL, Carroll FI, Kuhar MJ. Dopamine transporter synthesis and degradation rate in rat striatum and nucleus accumbens using RTI-76. Neuropharmacology 2000;39:578–85.

[15] Kimmel HL, Joyce AR, Carroll FI, Kuhar MJ. Dopamine D1 and D2 receptors influence dopamine transporter synthesis and degradation in the rat. J Pharmacol Exp Ther 2001;298:129–40.

[16] Kimmel HL, Carroll FI, Kuhar MJ. Withdrawal from repeated cocaine alters dopamine transporter protein turnover in the rat striatum. J Pharmacol Exp Ther 2003;304:15–21.

[17] Vicentic A, Battaglia G, Carroll FI, Kuhar MJ. Serotonin transporter production and degradation rates: studies with RTI-76. Brain Res 1999;841:1–10.

[18] Li LB, Chen N, Ramamoorthy S, Chi L, Cui XN, Wang LC, et al. The role of N-glycosylation in function and surface trafficking of the human dopamine transporter. J Biol Chem 2004;279:21012–20.

[19] Vaughan RA, Huff RA, Uhl GR, Kuhar MJ. Protein kinase C-mediated phosphorylation and functional regulation of dopamine transporters in striatal synaptosomes. J Biol Chem 1997;272:15541–6.

[20] Ramamoorthy S, Giovanetti E, Qian Y, Blakely RD. Phosphorylation and regulation of antidepressant-sensitive serotonin transporters. J Biol Chem 1998;273:2458–66.

[21] Jayanthi LD, Samuvel DJ, Ramamoorthy S. Regulated internalization and phosphorylation of the native norepinephrine transporter in response to phorbol esters. Evidence for localization in lipid rafts and lipid raft-mediated internalisation. J Biol Chem 2004;279:19315–26.

[22] Jayanthi LD, Ramamoorthy S. Regulation of monoamine transporters: influence of psychostimulants and therapeutic antidepressants. AAPS J 2005;7:E728–38.

[23] Apparsundaram S, Schroeter S, Giovanetti E, Blakely RD. Acute regulation of norepinephrine transport. II. PKC-modulated surface expression of human norepinephrine transporter proteins. J Pharmacol Exp Ther 1998;287:744–51.

[24] Apparsundaram S, Galli A, DeFelice LJ, Hartzell HC, Blakely RD. Acute regulation of norepinephrine transport. I. protein kinase C-linked muscarinic receptors influence transport capacity and transporter density in SK–N–SH cells. J Pharmacol Exp Ther 1998;287:733–43.

[25] Bauman AL, Apparsundaram S, Ramamoorthy S, Wadzinski BE, Vaughan RA, Blakely RD. Cocaine and antidepressant-sensitive biogenic amine transporters

exist in regulated complexes with protein phosphatase 2A. J Neurosci 2000;20:7571–8.
[26] Qian Y, Galli A, Ramamoorthy S, Risso S, DeFelice LJ, Blakely RD. Protein kinase C activation regulates human serotonin transporters in HEK-293 cells via altered cell surface expression. J Neurosci 1997;17:45–57.
[27] Zhu S-J, Kavanaugh MP, Sonders MS, Amara SG, Zahniser NR. Activation of protein kinase C inhibits uptake, currents and binding associated with the human dopamine transporter expressed in *Xenopus oocytes*. J Pharmacol Exp Ther 1997;282:1358–65.
[28] Pristupa ZB, McConkey F, Liu F, Man HY, Lee FJS, Wang Y, et al. Protein kinase-mediated bidirectional trafficking and functional regulation of the human dopamine transporter. Synapse 1998;30:79–87.
[29] Daniels GM, Amara SG. Regulated trafficking of the human dopamine transporter. Clathrin-mediated internalization and lysosomal degradation in response to phorbol esters. J Biol Chem 1999;274:35794–801.
[30] Melikian HE, Buckley KM. Membrane trafficking regulates the activity of the human dopamine transporter. J Neurosci 1999;19:7699–710.
[31] Kitayama S, Dohi T, Uhl GR. Phorbol esters alter functions of the expressed dopamine transporter. Eur J Pharmacol 1994;268:115–9.
[32] Zhang L, Coffey LL, Reith ME. Regulation of the functional activity of the human dopamine transporter by protein kinase C. Biochem Pharmacol 1997;53:677–88.
[33] Ramamoorthy S, Blakely RD. Phosphorylation and sequestration of serotonin transporters differentially modulated by psychostimulants. Science 1999;285:763–6.
[34] Foster JD, Pananusorn B, Vaughan RA. Dopamine transporters are phosphorylated on N-terminal serines in rat striatum. J Biol Chem 2002;277:25178–86.
[35] Bauman PA, Blakely RD. Determinants within the C-terminus of the human norepinephrine transporter dictate transporter trafficking, stability, and activity. Arch Biochem Biophys 2002;404:80–91.
[36] Melikian HE, McDonald JK, Gu H, Rudnick G, Moore KR, Blakely RD. Human norepinephrine transporter. Biosynthetic studies using a site-directed polyclonal antibody. J Biol Chem 1994;269:12290–7.
[37] Melikian HE, Ramamoorthy S, Tate CG, Blakely RD. Inability to *N*-glycosylate the human norepinephrine transporter reduces protein stability, surface trafficking, and transport activity but not ligand recognition. Mol Pharmacol 1996;50:266–76.
[38] Hahn MK, Robertson D, Blakely RD. A mutation in the human norepinephrine transporter gene (SLC6A2) associated with orthostatic intolerance disrupts surface expression of mutant and wild-type transporters. J Neurosci 2003;23:4470–8.
[39] Kitayama S, Ikeda T, Mitsuhata C, Sato T, Morita K, Dohi T. Dominant negative isoform of rat norepinephrine transporter produced by alternative RNA splicing. J Biol Chem 1999;274:10731–6.
[40] Sitte HH, Farhan H, Javitch JA. Sodium-dependent neurotransmitter transporters: oligomerization as a determinant of transporter function and trafficking. Mol Interv 2004;4:38–47.
[41] Torres GE, Carneiro A, Seamans K, Fiorentini C, Sweeney A, Yao WD, et al. Oligomerization and trafficking of the human dopamine transporter. Mutational analysis identifies critical domains important for the functional expression of the transporter. J Biol Chem 2003;278: 2731–9.
[42] Hastrup H, Karlin A, Javitch JA. Symmetrical dimer of the human dopamine transporter revealed by cross-linking Cys-306 at the extracellular end of the sixth transmembrane segment. Proc Natl Acad Sci USA 2001;98:10055–60.
[43] Just H, Sitte HH, Schmid JA, Freissmuth M, Kudlacek O. Identification of an additional interaction domain in transmembrane domains 11 and 12 that supports oligomer formation in the human serotonin transporter. J Biol Chem 2004;279:6650–7.
[44] Kilic F, Rudnick G. Oligomerization of serotonin transporter and its functional consequences. Proc Natl Acad Sci USA 2000;97:3106–11.
[45] Kocabas AM, Rudnick G, Kilic F. Functional consequences of homo- but not hetero-oligomerization between transporters for the biogenic amine neurotransmitters. J Neurochem 2003;85:1513–20.
[46] Chi L, Reith ME. Substrate-induced trafficking of the dopamine transporter in heterologously expressing cells and in rat striatal synaptosomal preparations. J Pharmacol Exp Ther 2003;307:729–36.
[47] Bolan EA, Kivell B, Jaligam V, Oz M, Jayanthi LD, Han Y, et al. D2 receptors regulate dopamine transporter function via an extracellular signal-regulated kinases 1 and 2-dependent and phosphoinositide 3 kinase-independent mechanism. Mol Pharmacol 2007;71:1222–32.
[48] Lester HA, Mager S, Quick MW, Corey JL. Permeation properties of neurotransmitter transporters. Annu Rev Pharmacol Toxicol 1994;34:219–49.
[49] Sonders MS, Zhu SJ, Zahniser NR, Kavanaugh MP, Amara SG. Multiple ionic conductances of the human dopamine transporter: the actions of dopamine and psychostimulants. J Neurosci 1997;17:960–74.
[50] Zahniser NR, Gerhardt GA, Hoffman AF, Lupica CR. Voltage-dependency of the dopamine transporter in rat brain. Adv Pharmacol 1998;42:195–8.
[51] Amara SG, Kuhar MJ. Neurotransmitter transporters: recent progress. Annu Rev Neurosci 1993;16:73–93.
[52] Cases O, Lebrand C, Giros B, Vitalis T, De Maeyer E, Caron MG, et al. Plasma membrane transporters of serotonin, dopamine, and norepinephrine mediate serotonin accumulation in atypical locations in the developing brain of monoamine oxidase A knock-outs. J Neurosci 1998;18:6914–27.
[53] Pan Y, Gembom E, Peng W, Lesch KP, Mossner R, Simantov R. Plasticity in serotonin uptake in primary neuronal cultures of serotonin transporter knockout mice.. Brain Res Dev Brain Res 2001;126:125–9.
[54] Moron JA, Brockington A, Wise RA, Rocha BA, Hope BT. Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knock-out mouse lines. J Neurosci 2002;22:389–95.
[55] Mossner R, Simantov R, Marx A, Lesch KP, Seif I. Aberrant accumulation of serotonin in dopaminergic neurons. Neurosci Lett 2006;401:49–54.
[56] Bonisch H. The role of co-transported sodium in the effect of indirectly acting sympathomimetic amines. Naunyn Schmiedebergs Arch Pharmacol 1986;332:135–41.
[57] Bonisch H, Bruss M. The noradrenaline transporter of the neuronal plasma membrane. Ann NY Acad Sci 1994;733:193–202.
[58] Gresch PJ, Sved AF, Zigmond MJ, Finlay JM. Local influence of endogenous norepinephrine on extracellular dopamine in rat medial prefrontal cortex. J Neurochem 1995;65: 111–6.
[59] Carboni E, Tanda GL, Frau R, Di Chiara G. Blockade of the noradrenaline carrier increases extracellular dopamine concentrations in the prefrontal cortex: evidence that dopamine is taken up in vivo by noradrenergic terminals. J Neurochem 1990;55:1067–70.

[60] Yelin R, Schuldiner S. Vesicular neurotransmitter transporters: pharmacology, biochemistry, and molecular analysis. In: Reith MEA, editor. Neurotransmitter transporters: structure, function, and regulation. Totowa, NJ: Humana Press; 2002. p. 313–54.
[61] Schuldiner S, Shirvan A, Linial M. Vesicular neurotransmitter transporters: from bacteria to humans. Physiol Rev 1995;75:369–92.
[62] Erickson JD, Eiden LE, Hoffman BJ. Expression cloning of a reserpine-sensitive vesicular monoamine transporter. Proc Natl Acad Sci USA 1992;89:10993–7.
[63] Liu Y, Peter D, Roghani A, Schuldiner S, Prive GG, Eisenberg D, et al. A cDNA that suppresses MPP+ toxicity encodes a vesicular amine transporter. Cell 1992;70: 539–51.
[64] Riddle EL, Fleckenstein AE, Hanson GR. Role of monoamine transporters in mediating psychostimulant effects. AAPS J 2005;7:E847–51.
[65] Fleckenstein AE, Hanson GR. Impact of psychostimulants on vesicular monoamine transporter function. Eur J Pharmacol 2003;479:283–9.
[66] Liu Y, Edwards RH. The role of vesicular transport proteins in synaptic transmission and neural degeneration. Annu Rev Neurosci 1997;20:125–56.
[67] Henry JP, Sagne C, Bedet C, Gasnier B. The vesicular monoamine transporter: from chromaffin granule to brain. Neurochem Int 1998;32:227–46.
[68] Johnson Jr RG. Accumulation of biological amines into chromaffin granules: a model for hormone and neurotransmitter transport. Physiol Rev 1988;68:232–307.
[69] Greengard P. The neurobiology of dopamine signaling. Biosci Rep 2001;21:247–69.
[70] Uhl G, Lin Z, Metzger T, Dar DE. Dopamine transporter mutants, small molecules, and approaches to cocaine antagonist/dopamine transporter disinhibitor development. Methods Enzymol 1998;296:456–65.
[71] Westerink RH. Targeting exocytosis: ins and outs of the modulation of quantal dopamine release. CNS Neurol Disord Drug Targets 2006;5:57–77.
[72] Lin Z, Madras BK. Human genetics and pharmacology of neurotransmitter transporters. Handb Exp Pharmacol 2006;327–71.
[73] Nirenberg MJ, Chan J, Vaughan RA, Uhl GR, Kuhar MJ, Pickel VM. Immunogold localization of the dopamine transporter: an ultrastructural study of the rat ventral tegmental area. J Neurosci 1997;17:5255–62.
[74] Sesack SR, Hawrylak VA, Guido MA, Levey AI. Cellular and subcellular localization of the dopamine transporter in rat cortex. Adv Pharmacol 1998;42:171–4.
[75] Ciliax BJ, Heilman C, Demchyshyn LL, Pristupa ZB, Ince E, Hersch SM, et al. The dopamine transporter: immunochemical characterization and localization in brain. J Neurosci 1995;15:1714–23.
[76] Barnes NM, Sharp T. A review of central 5-HT receptors and their function. Neuropharmacology 1999;38:1083–152.
[77] Hoyer D, Hannon JP, Martin GR. Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol Biochem Behav 2002;71:533–54.
[78] Jacobs BL, Azmitia EC. Structure and function of the brain serotonin system. Physiol Rev 1992;72:165–229.
[79] Varnas K, Halldin C, Hall H. Autoradiographic distribution of serotonin transporters and receptor subtypes in human brain. Hum Brain Mapp 2004;22:246–60.
[80] Smith HR, Daunais JB, Nader MA, Porrino LJ. Distribution of [3H]citalopram binding sites in the nonhuman primate brain. Ann NY Acad Sci 1999;877:700–2.
[81] Astier B, Van Bockstaele EJ, Aston-Jones G, Pieribone VA. Anatomical evidence for multiple pathways leading from the rostral ventrolateral medulla (nucleus paragigantocellularis) to the locus coeruleus in rat. Neurosci Lett 1990;118:141–6.
[82] Grant SJ, Aston-Jones G, Redmond Jr DE. Responses of primate locus coeruleus neurons to simple and complex sensory stimuli. Brain Res Bull 1988;21:401–10.
[83] Carpenter MB, Sutin J. Human neuroanatomy. Baltimore: Williams & Wilkins; 1983.
[84] Donnan GA, Kaczmarczyk SJ, Paxinos G, Chilco PJ, Kalnins RM, Woodhouse DG, et al. Distribution of catecholamine uptake sites in human brain as determined by quantitative [3H] mazindol autoradiography. J Comp Neurol 1991;304:419–34.
[85] Hoffman BJ, Hansson SR, Mezey E, Palkovits M. Localization and dynamic regulation of biogenic amine transporters in the mammalian central nervous system. Front Neuroendocrinol 1998;19:187–231.
[86] Erickson JD, Schafer MK, Bonner TI, Eiden LE, Weihe E. Distinct pharmacological properties and distribution in neurons and endocrine cells of two isoforms of the human vesicular monoamine transporter. Proc Natl Acad Sci USA 1996;93:5166–71.
[87] Peter D, Liu Y, Sternini C, de Giorgio R, Brecha N, Edwards RH. Differential expression of two vesicular monoamine transporters. J Neurosci 1995;15:6179–88.
[88] Hahn MK, Blakely RD. The functional impact of SLC6 transporter genetic variation. Annu Rev Pharmacol Toxicol 2007;47:401–41.
[89] Hediger MA, Romero MF, Peng JB, Rolfs A, Takanaga H, Bruford EA. The ABCs of solute carriers: physiological, pathological and therapeutic implications of human membrane transport proteinsIntroduction. Pflugers Arch 2004;447:465–8.
[90] Erickson JD, Eiden LE. Functional identification and molecular cloning of a human brain vesicle monoamine transporter. J Neurochem 1993;61:2314–7.
[91] Grunhage F, Schulze TG, Muller DJ, Lanczik M, Franzek E, Albus M, et al. Systematic screening for DNA sequence variation in the coding region of the human dopamine transporter gene (DAT1). Mol Psychiatry 2000;5:275–82.
[92] Mazei-Robison MS, Couch RS, Shelton RC, Stein MA, Blakely RD. Sequence variation in the human dopamine transporter gene in children with attention deficit hyperactivity disorder. Neuropharmacology 2005;49:724–36.
[93] Lin Z, Uhl GR. Human dopamine transporter gene variation: effects of protein coding variants V55A and V382A on expression and uptake activities. Pharmacogenomics J 2003;3:159–68.
[94] Mazei-Robison MS, Blakely RD. Expression studies of naturally occurring human dopamine transporter variants identifies a novel state of transporter inactivation associated with Val382Ala. Neuropharmacology 2005;49:737–49.
[95] Kilic F, Murphy DL, Rudnick G. A human serotonin transporter mutation causes constitutive activation of transport activity. Mol Pharmacol 2003;64:440–6.
[96] Ozaki N, Goldman D, Kaye WH, Plotnicov K, Greenberg BD, Lappalainen J, et al. Serotonin transporter missense mutation associated with a complex neuropsychiatric phenotype. Mol Psychiatry 2003;8:933–6.
[97] Jacob G, Shannon JR, Costa F, Furlan R, Biaggioni I, Mosqueda-Garcia R, et al. Abnormal norepinephrine clearance and adrenergic receptor sensitivity in idiopathic orthostatic intolerance. Circulation 1999;99:1706–12.
[98] Shannon JR, Flattem NL, Jordan J, Jacob G, Black BK, Biaggioni I, et al. Orthostatic intolerance and tachycardia associated with norepinephrine-transporter deficiency. N Engl J Med 2000;342:541–9.

[99] Bly M. Mutation in the vesicular monoamine gene, SLC18A1, associated with schizophrenia. Schizophr Res 2005;78:337–8.
[100] Richards M, Iijima Y, Kondo H, Shizuno T, Hori H, Arima K, et al. Association study of the vesicular monoamine transporter 1 (VMAT1) gene with schizophrenia in a Japanese population. Behav Brain Funct 2006;2:39.
[101] Han DD, Gu HH. Comparison of the monoamine transporters from human and mouse in their sensitivities to psychostimulant drugs. BMC Pharmacol 2006;6:6.
[102] Fleckenstein AE, Gibb JW, Hanson GR. Differential effects of stimulants on monoaminergic transporters: pharmacological consequences and implications for neurotoxicity. Eur J Pharmacol 2000;406:1–13.
[103] Rothman RB, Baumann MH. Monoamine transporters and psychostimulant drugs. Eur J Pharmacol 2003;479:23–40.
[104] Rudnick G, Clark J. From synapse to vesicle: the reuptake and storage of biogenic amine neurotransmitters. Biochim Biophys Acta 1993;1144:249–63.
[105] Rudnick G. Mechanisms of biogenic amine transporters. In: Reith M, editor. Neurotransmitter transporters: structure, function, and regulation. Totowa, NY: Humana Press; 1997. p. 73–100.
[106] Tzschentke TM, Schmidt WJ. Functional relationship among medial prefrontal cortex, nucleus accumbens, and ventral tegmental area in locomotion and reward. Crit Rev Neurobiol 2000;14:131–42.
[107] Tzschentke TM. Pharmacology and behavioral pharmacology of the mesocortical dopamine system. Prog Neurobiol 2001;63:241–320.
[108] Civelli O, Bunzow JR, Grandy DK, Zhou QY, Van Tol HH. Molecular biology of the dopamine receptors. Eur J Pharmacol 1991;207:277–86.
[109] Schwartz J, Giros B, Martres M, Sokoloff P. The dopamine receptor family: molecular biology and pharmacology. Neurosciences 1992;4:99–108.
[110] Spealman RD, Bergman J, Madras BK, Kamien JB, Melia KF. Role of D1 and D2 dopamine receptors in the behavioral effects of cocaine. Neurochem Int 1992;20. Suppl:147S-S152.
[111] Woolverton WL, Johnson KM. Neurobiology of cocaine abuse. Trends Pharmacol Sci 1992;13:193–200.
[112] Mello NK, Negus SS. Preclinical evaluation of pharmacotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures. Neuropsychopharmacology 1996;14:375–424.
[113] Cline EJ, Scheffel U, Boja JW, Carroll FI, Katz JL, Kuhar MJ. Behavioral effects of novel cocaine analogs: a comparison with in vivo receptor binding potency. J Pharmacol Exp Ther 1992;260:1174–9.
[114] Kuhar MJ. Neurotransmitter transporters as drug targets: recent research with a focus on the dopamine transporter. Pharmacologist 1993;35:28–33.
[115] Katz JL, Izenwasser S, Terry P. Relationships among dopamine transporter affinities and cocaine-like discriminative-stimulus effects. Psychopharmacology 2000;148:90–8.
[116] Bergman J, Madras BK, Johnson SE, Spealman RD. Effects of cocaine and related drugs in nonhuman primates. III. Self-administration by squirrel monkeys. J Pharmacol Exp Ther 1989;251:150–5.
[117] Madras BK, Fahey MA, Bergman J, Canfield DR, Spealman RD. Effects of cocaine and related drugs in nonhuman primates. I. [3H]cocaine binding sites in caudate-putamen. J Pharmacol Exp Ther 1989;251:131–41.
[118] Spealman RD, Madras BK, Bergman J. Effects of cocaine and related drugs in nonhuman primates. II. Stimulant effects on scheduled-controlled behavior. J Pharmacol Exp Ther 1989;251:142–9.
[119] Howell LL, Byrd LD. Characterization of the effects of cocaine and GBR 12909, a dopamine uptake inhibitor, on behavior in the squirrel monkey. J Pharmacol Exp Ther 1991;258:178–85.
[120] Nader MA, Grant KA, Davies HM, Mach RH, Childers SR. The reinforcing and discriminative stimulus effects of the novel cocaine analog 2beta-propanoyl-3beta-(4-tolyl)-tropane in rhesus monkeys. J Pharmacol Exp Ther 1997;280:541–50.
[121] Howell LL, Czoty PW, Byrd LD. Pharmacological interactions between serotonin and dopamine on behavior in the squirrel monkey. Psychopharmacology (Berlin) 1997;131:40–8.
[122] Howell LL, Czoty PW, Kuhar MJ, Carroll FI. Comparative behavioral pharmacology of cocaine and the selective dopamine uptake inhibitor RTI-113 in the squirrel monkey. J Pharmacol Exp Ther 2000;292:521–9.
[123] Self DW, Stein L. The D1 agonists SKF 82958 and SKF 77434 are self-administered by rats. Brain Res 1992;582:349–52.
[124] Woolverton WL, Goldberg LI, Ginos JZ. Intravenous self-administration of dopamine receptor agonists by rhesus monkeys. Psychopharmacology 1984;123:34–41.
[125] Weed MR, Woolverton WL. The reinforcing effects of dopamine D1 receptor agonists in rhesus monkeys. J Pharmacol Exp Ther 1995;275:1367–74.
[126] Woolverton WL. Effects of a D1 and a D2 dopamine antagonist on the self-administration of cocaine and piribedil by rhesus monkeys. Pharmacol Biochem Behav 1986;24:531–5.
[127] Barrett RL, Appel JB. Effects of stimulation and blockade of dopamine receptor subtypes on the discriminative stimulus properties of cocaine. Psychopharmacology (Berlin) 1989;99:13–6.
[128] Callahan PM, Appel JB, Cunningham KA. Dopamine D1 and D2 mediation of the discriminative stimulus properties of d-amphetamine and cocaine. Psychopharmacology 1991;103:50–5.
[129] Kleven MS, Anthony EW, Goldberg LI, Woolverton WL. Blockade of the discriminative stimulus effects of cocaine in rhesus monkeys with the D1 dopamine antagonist SCH 23390. Psychopharmacology (Berlin) 1988;95:427–9.
[130] Bergman J, Spealman RD. Behavioral effects of histamine H1 antagonists: comparison with other drugs and modification by haloperidol. J Pharmacol Exp Ther 1988;245:471–8.
[131] Howell LL, Byrd LD. Enhanced sensitivity to the behavioral effects of cocaine after chronic administration of D2-selective dopamine antagonists in the squirrel monkey. J Pharmacol Exp Ther 1992;262:907–15.
[132] Spealman RD. Antagonism of behavioral effects of cocaine by selective dopamine receptor blockers. Psychopharmacology (Berlin) 1990;101:142–5.
[133] Volkow ND, Wang GJ, Fischman MW, Foltin RW, Fowler JS, Abumrad NN, et al. Relationship between subjective effects of cocaine and dopamine transporter occupancy. Nature 1997;386:827–30.
[134] Volkow ND, Wang GJ, Fowler JS, Gatley SJ, Logan J, Ding YS, et al. Blockade of striatal dopamine transporters by intravenous methylphenidate is not sufficient to induce self-reports of "high". J Pharmacol Exp Ther 1999;288:14–20.
[135] Volkow ND, Gatley SJ, Fowler JS, Logan J, Fischman M, Gifford AN, et al. Cocaine doses equivalent to those abused by humans occupy most of the dopamine transporters. Synapse 1996;24:399–402.
[136] Wilcox KM, Lindsey KP, Votaw JR, Goodman MM, Martarello L, Carroll FI, et al. Self-administration of cocaine and the cocaine analog RTI-113: relationship to dopamine transporter occupancy determined by PET neuroimaging in rhesus monkeys. Synapse 2002;43:78–85.

[137] Lindsey KP, Wilcox KM, Votaw JR, Goodman MM, Plisson C, Carroll FI, et al. Effects of dopamine transporter inhibitors on cocaine self-administration in rhesus monkeys: relationship to transporter occupancy determined by positron emission tomography neuroimaging. J Pharmacol Exp Ther 2004;309:959–69.
[138] Villemagne VL, Rothman RB, Yokoi F, Rice KC, Matecka D, Dannals RF, et al. Doses of GBR12909 that suppress cocaine self-administration in non-human primates substantially occupy dopamine transporters as measured by [11C] WIN35,428 PET scans. Synapse 1999;32:44–50.
[139] Vanover KE, Nader MA, Woolverton WL. Evaluation of the discriminative stimulus and reinforcing effects of sertraline in rhesus monkeys. Pharmacol Biochem Behav 1992;41:789–93.
[140] Howell LL, Byrd LD. Serotonergic modulation of the behavioral effects of cocaine in the squirrel monkey. J Pharmacol Exp Ther 1995;275:1551–9.
[141] Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 1987;237:1219–23.
[142] Ritz MC, Kuhar MJ. Relationship between self-administration of amphetamine and monoamine receptors in brain: comparison with cocaine. J Pharmacol Exp Ther 1989;248:1010–7.
[143] Baumann MH, Ayestas MA, Dersch CM, Brockington A, Rice KC, Rothman RB. Effects of phentermine and fenfluramine on extracellular dopamine and serotonin in rat nucleus accumbens: therapeutic implications. Synapse 2000;36:102–13.
[144] Glatz AC, Ehrlich M, Bae RS, Clarke MJ, Quinlan PA, Brown EC, et al. Inhibition of cocaine self-administration by fluoxetine or D-fenfluramine combined with phentermine. Pharmacol Biochem Behav 2002;71:197–204.
[145] Wee S, Anderson KG, Baumann MH, Rothman RB, Blough BE, Woolverton WL. Relationship between the serotonergic activity and reinforcing effects of a series of amphetamine analogs. J Pharmacol Exp Ther 2005;313:848–54.
[146] Ginsburg BC, Kimmel HL, Carroll FI, Goodman MM, Howell LL. Interaction of cocaine and dopamine transporter inhibitors on behavior and neurochemistry in monkeys. Pharmacol Biochem Behav 2005;80:481–91.
[147] Carroll ME, Lac ST, Asencio M, Kragh R. Fluoxetine reduces intravenous cocaine self-administration in rats. Pharmacol Biochem Behav 1990;35:237–44.
[148] Porrino LJ, Ritz MC, Goodman NL, Sharpe LG, Kuhar MJ, Goldberg SR. Differential effects of the pharmacological manipulation of serotonin systems on cocaine and amphetamine self-administration in rats. Life Sci 1989;45:1529–35.
[149] Kleven MS, Woolverton WL. Effects of three monoamine uptake inhibitors on behavior maintained by cocaine or food presentation in rhesus monkeys. Drug Alcohol Depend 1993;31:149–58.
[150] Spealman RD. Modification of behavioral effects of cocaine by selective serotonin and dopamine uptake inhibitors in squirrel monkeys. Psychopharmacology (Berlin) 1993;112:93–9.
[151] Czoty PW, Ginsburg BC, Howell LL. Serotonergic attenuation of the reinforcing and neurochemical effects of cocaine in squirrel monkeys. J Pharmacol Exp Ther 2002;300:831–7.
[152] Howell LL, Hoffman JM, Votaw JR, Landrum AM, Wilcox KM, Lindsey KP. Cocaine-induced brain activation determined by positron emission tomography neuroimaging in conscious rhesus monkeys. Psychopharmacology (Berlin) 2002;159:154–60.
[153] Howell LL, Carroll FI, Votaw JR, Goodman MM, Kimmel HL. Effects of combined dopamine and serotonin transporter inhibitors on cocaine self-administration in rhesus monkeys. J Pharmacol Exp Ther 2007;320:757–65.
[154] Herve D, Pickel VM, Joh TH, Beaudet A. Serotonin axon terminals in the ventral tegmental area of the rat: fine structure and synaptic input to dopaminergic neurons. Brain Res 1987;435:71–83.
[155] Phelix CF, Broderick PA. Light microscopic immunocytochemical evidence of converging serotonin and dopamine terminals in ventrolateral nucleus accumbens. Brain Res Bull 1995;37:37–40.
[156] Di Matteo V, De Blasi A, Di Giulio C, Esposito E. Role of 5-HT(2C) receptors in the control of central dopamine function. Trends Pharmacol Sci 2001;22:229–32.
[157] Di Mascio M, Di Giovanni G, Di Matteo V, Prisco S, Esposito E. Selective serotonin reuptake inhibitors reduce the spontaneous activity of dopaminergic neurons in the ventral tegmental area.. Brain Res Bull 1998;46:547–54.
[158] Prisco S, Pagannone S, Esposito E. Serotonin-dopamine interaction in the rat ventral tegmental area: an electrophysiological study in vivo. J Pharmacol Exp Ther 1994;271:83–90.
[159] Di Matteo V, Di Giovanni G, Di Mascio M, Esposito E. Biochemical and electrophysiological evidence that RO 60-0175 inhibits mesolimbic dopaminergic function through serotonin(2C) receptors. Brain Res 2000;865:85–90.
[160] Ashby C, Minabe Y. Differential effect of the 5-HT2C/2B antagonist SB200646 and the selective 5-HT2A antagonist MDL 100907 on midbrain dopamine neurons in rats: An electrophysiological study. Soc Neurosci Abstr 1996;22:1723.
[161] Di Matteo V, Di Giovanni G, Di Mascio M, Esposito E. SB 242084, a selective serotonin2C receptor antagonist, increases dopaminergic transmission in the mesolimbic system. Neuropharmacology 1999;38:1195–205.
[162] Eberle-Wang K, Mikeladze Z, Uryu K, Chesselet MF. Pattern of expression of the serotonin2C receptor messenger RNA in the basal ganglia of adult rats. J Comp Neurol 1997;384:233–47.
[163] Cameron DL, Williams JT. Cocaine inhibits GABA release in the VTA through endogenous 5-HT. J Neurosci 1994;14:6763–7.
[164] Blandina P, Goldfarb J, Craddock-Royal B, Green JP. Release of endogenous dopamine by stimulation of 5-hydroxytryptamine3 receptors in rat striatum. J Pharmacol Exp Ther 1989;251:803–9.
[165] De Deurwaerdere P, L'Hirondel M, Bonhomme N, Lucas G, Cheramy A, Spampinato U. Serotonin stimulation of 5-HT4 receptors indirectly enhances in vivo dopamine release in the rat striatum. J Neurochem 1997;68:195–203.
[166] Parsons LH, Weiss J, Koob GF. Serotonin$_{1B}$ receptor stimulation enhances cocaine reinforcement. J Neurosci 1998;18:10078–89.
[167] Layer RT, Uretsky NJ, Wallace LJ. Effect of serotonergic agonists in the nucleus accumbens on d-amphetamine-stimulated locomotion. Life Sci 1992;50:813–20.
[168] Kankaanpaa A, Lillsunde P, Ruotsalainen M, Ahtee L, Seppala T. 5-HT3 receptor antagonist MDL 72222 dose-dependently attenuates cocaine- and amphetamine-induced elevations of extracellular dopamine in the nucleus accumbens and the dorsal striatum. Pharmacol Toxicol 1996;78:317–21.
[169] Berridge CW, Stratford TL, Foote SL, Kelley AE. Distribution of dopamine beta-hydroxylase-like immunoreactive fibers within the shell subregion of the nucleus accumbens. Synapse 1997;27:230–41.
[170] Delfs JM, Zhu Y, Druhan JP, Aston-Jones GS. Origin of noradrenergic afferents to the shell subregion of the

nucleus accumbens: anterograde and retrograde tract-tracing studies in the rat. Brain Res 1998;806:127–40.
[171] Liprando LA, Miner LH, Blakely RD, Lewis DA, Sesack SR. Ultrastructural interactions between terminals expressing the norepinephrine transporter and dopamine neurons in the rat and monkey ventral tegmental area. Synapse 2004;52:233–44.
[172] Grenhoff J, Nisell M, Ferre S, Aston-Jones G, Svensson TH. Noradrenergic modulation of midbrain dopamine cell firing elicited by stimulation of the locus coeruleus in the rat. J Neural Transm Gen Sect 1993;93:11–25.
[173] Lategan AJ, Marien MR, Colpaert FC. Effects of locus coeruleus lesions on the release of endogenous dopamine in the rat nucleus accumbens and caudate nucleus as determined by intracerebral microdialysis. Brain Res 1990;523:134–8.
[174] Ventura R, Cabib S, Alcaro A, Orsini C, Puglisi-Allegra S. Norepinephrine in the prefrontal cortex is critical for amphetamine-induced reward and mesoaccumbens dopamine release. J Neurosci 2003;23:1879–85.
[175] Drouin C, Darracq L, Trovero F, Blanc G, Glowinski J, Cotecchia S, et al. Alpha1b-adrenergic receptors control locomotor and rewarding effects of psychostimulants and opiates. J Neurosci 2002;22:2873–84.
[176] Drouin C, Blanc G, Villegier AS, Glowinski J, Tassin JP. Critical role of alpha1-adrenergic receptors in acute and sensitized locomotor effects of D-amphetamine, cocaine, and GBR 12783: influence of preexposure conditions and pharmacological characteristics. Synapse 2002;43: 51–61.
[177] Weinshenker D, Miller NS, Blizinsky K, Laughlin ML, Palmiter RD. Mice with chronic norepinephrine deficiency resemble amphetamine-sensitized animals. Proc Natl Acad Sci USA 2002;99:13873–7.
[178] Erb S, Hitchcott PK, Rajabi H, Mueller D, Shaham Y, Stewart J. *Alpha*-2 adrenergic receptor agonists block stress-induced reinstatement of cocaine-seeking. Neuropsychopharmacology 2000;23:138–50.
[179] Spealman RD. Noradrenergic involvement in the discriminative stimulus effects of cocaine in squirrel monkeys. J Pharmacol Exp Ther 1995;275:53–62.
[180] Lee B, Tiefenbacher S, Platt DM, Spealman RD. Pharmacological blockade of alpha2-adrenoceptors induces reinstatement of cocaine-seeking behavior in squirrel monkeys. Neuropsychopharmacology 2004;29:686–93.
[181] Platt DM, Rowlett JK, Spealman RD. Noradrenergic mechanisms in cocaine-induced reinstatement of drug seeking in squirrel monkeys. J Pharmacol Exp Ther 2007;322:894–902.
[182] Rothman RB, Baumann MH, Dersch CM, Romero DV, Rice KC, Carroll FI, et al. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. Synapse 2001;39:32–41.
[183] Tella SR. Effects of monoamine reuptake inhibitors on cocaine self-administration in rats. Pharmacol Biochem Behav 1995;51:687–92.
[184] Woolverton WL. Evaluation of the role of norepinephrine in the reinforcing effects of psychomotor stimulants in rhesus monkeys. Pharmacol Biochem Behav 1987;26: 835–9.
[185] Kleven MS, Woolverton WL. Effects of bromocriptine and desipramine on behavior maintained by cocaine or food presentation in rhesus monkeys. Psychopharmacology (Berlin) 1990;101:208–13.
[186] Mello NK, Lukas SE, Bree MP, Mendelson JH. Desipramine effects on cocaine self-administration by rhesus monkeys. Drug Alcohol Depend 1990;26:103–16.
[187] Sesack SR, Carr DB, Omelchenko N, Pinto A. Anatomical substrates for glutamate-dopamine interactions: evidence for specificity of connections and extrasynaptic actions. Ann N Y Acad Sci 2003;1003:36–52.
[188] Pierce RC, Bell K, Duffy P, Kalivas PW. Repeated cocaine augments excitatory amino acid transmission in the nucleus accumbens only in rats having developed behavioral sensitization. J Neurosci 1996;16:1550–60.
[189] Cornish JL, Kalivas PW. Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. J Neurosci (Online) 2000;20:RC89.
[190] Cornish JL, Kalivas PW. Cocaine sensitization and craving: differing roles for dopamine and glutamate in the nucleus accumbens. J Addict Dis 2001;20:43–54.
[191] Carlezon Jr WA, Nestler EJ. Elevated levels of GluR1 in the midbrain: a trigger for sensitization to drugs of abuse? Trends Neurosci 2002;25:610–5.
[192] Harris GC, Aston-Jones G. Critical role for ventral tegmental glutamate in preference for a cocaine-conditioned environment. Neuropsychopharmacology 2003;28:73–6.
[193] Battaglia G, Monn JA, Schoepp DD. In vivo inhibition of veratridine-evoked release of striatal excitatory amino acids by the group II metabotropic glutamate receptor agonist LY354740 in rats. Neurosci Lett 1997;229:161–4.
[194] Moghaddam B, Adams BW. Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. Science 1998;281:1349–52.
[195] Hu G, Duffy P, Swanson C, Ghasemzadeh MB, Kalivas PW. The regulation of dopamine transmission by metabotropic glutamate receptors. J Pharmacol Exp Ther 1999;289:412–6.
[196] Xi ZX, Baker DA, Shen H, Carson DS, Kalivas PW. Group II metabotropic glutamate receptors modulate extracellular glutamate in the nucleus accumbens. J Pharmacol Exp Ther 2002;300:162–71.
[197] Baker DA, Xi ZX, Shen H, Swanson CJ, Kalivas PW. The origin and neuronal function of in vivo nonsynaptic glutamate. J Neurosci 2002;22:9134–41.
[198] Baker DA, McFarland K, Lake RW, Shen H, Tang XC, Toda S, et al. Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. Nat Neurosci 2003;6:743–9.
[199] Xi ZX, Ramamoorthy S, Baker DA, Shen H, Samuvel DJ, Kalivas PW. Modulation of group II metabotropic glutamate receptor signaling by chronic cocaine. J Pharmacol Exp Ther 2002;303:608–15.
[200] Vezina P, Suto N. Glutamate and the self-administration of psychomotor-stimulant drugs. In: Herman BH, editor. Glutamate and addiction. Totowa, NJ: Humana Press; 2002 p. 183–200.
[201] Kalivas PW, McFarland K, Bowers S, Szumlinski K, Xi ZX, Baker D. Glutamate transmission and addiction to cocaine. Ann NY Acad Sci 2003;1003:169–75.
[202] McFarland K, Lapish CC, Kalivas PW. Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. J Neurosci 2003;23:3531–7.
[203] Lee B, Platt DM, Rowlett JK, Adewale AS, Spealman RD. Attenuation of behavioral effects of cocaine by the metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)-pyridine in squirrel monkeys: comparison with dizocilpine. J Pharmacol Exp Ther 2005;312:1232–40.
[204] Dewey SL, Smith GS, Logan J, Brodie JD, Yu DW, Ferrieri RA, et al. GABAergic inhibition of endogenous dopamine release measured in vivo with 11C-raclopride and positron emission tomography. J Neurosci 1992;12:3773–80.
[205] Churchill L, Dilts RP, Kalivas PW. Autoradiographic localization of gamma-aminobutyric acidA receptors

within the ventral tegmental area. Neurochem Res 1992;17:101–6.
[206] White FJ. Synaptic regulation of mesocorticolimbic dopamine neurons. Annu Rev Neurosci 1996;19:405–36.
[207] Steffensen SC, Svingos AL, Pickel VM, Henriksen SJ. Electrophysiological characterization of GABAergic neurons in the ventral tegmental area. J Neurosci 1998;18:8003–15.
[208] Kita H, Kitai ST. Glutamate decarboxylase immunoreactive neurons in rat neostriatum: their morphological types and populations. Brain Res 1988;447:346–52.
[209] Roberts DC, Brebner K. GABA modulation of cocaine self-administration. Ann NY Acad Sci 2000;909:145–58.
[210] Cousins MS, Roberts DC, de Wit H. GABA(B) receptor agonists for the treatment of drug addiction: a review of recent findings. Drug Alcohol Depend 2002;65:209–20.
[211] Dewey SL, Chaurasia CS, Chen CE, Volkow ND, Clarkson FA, Porter SP, et al. GABAergic attenuation of cocaine-induced dopamine release and locomotor activity. Synapse 1997;25:393–8.
[212] Morgan AE, Dewey SL. Effects of pharmacologic increases in brain GABA levels on cocaine-induced changes in extracellular dopamine. Synapse 1998;28:60–5.
[213] Shoaib M, Swanner LS, Beyer CE, Goldberg SR, Schindler CW. The $GABA_B$ agonist baclofen modifies cocaine self-adminstration in rats. Behav Pharmacol 1998;9:195–206.
[214] Brebner K, Phelan R, Roberts DCS. Effect of baclofen on cocaine self-administration in rats reinforced under fixed-ratio 1 and progressive-ratio schedules. Psychopharmacology 2000;148:314–21.
[215] Campbell UC, Lac ST, Carroll ME. Effects of baclofen on maintenance and reinstatement of intravenous cocaine self-administration in rats. Psychopharmacology (Berlin) 1999;143:209–14.
[216] Dewey SL, Morgan AE, Ashby Jr CR, Horan B, Kushner SA, Logan J, et al. A novel strategy for the treatment of cocaine addiction. Synapse 1998;30:119–29.
[217] Kushner SA, Dewey SL, Kornetsky C. The irreversible gamma-aminobutyric acid (GABA) transaminase inhibitor gamma-vinyl-GABA blocks cocaine self-administration in rats. J Pharmacol Exp Ther 1999;290:797–802.
[218] Kushner SA, Dewey SL, Kornetsky C. Gamma-vinyl GABA attenuates cocaine-induced lowering of brain stimulation reward thresholds. Psychopharmacology (Berlin) 1997;133:383–8.
[219] Woolverton WL, Weiss SRB. Tolerance and sensitization to cocaine: an integrated view. In: Higgins ST, Katz JL, editors. Cocaine abuse: behavior, pharmacology, and clinical applications. San Diego: Academic Press; 1998. p. 107–34.
[220] Robinson TE, Berridge KC. The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction 2000;95(Suppl. 2):S91–117.
[221] Wolf ME, Sun X, Mangiavacchi S, Chao SZ. Psychomotor stimulants and neuronal plasticity. Neuropharmacology 2004;47(Suppl. 1):61–79.
[222] Stewart J, Vezina P. Microinjections of SCH-23390 into the ventral tegmental area and substantia nigra pars reticulata attenuate the development of sensitization to the locomotor activating effects of systemic amphetamine. Brain Res 1989;495:401–6.
[223] Vezina P. D1 dopamine receptor activation is necessary for the induction of sensitization by amphetamine in the ventral tegmental area. J Neurosci 1996;16:2411–20.
[224] Kalivas PW, Alesdatter JE. Involvement of N-methyl-D-aspartate receptor stimulation in the ventral tegmental area and amygdala in behavioral sensitization to cocaine. J Pharmacol Exp Ther 1993;267:486–95.
[225] Wolf ME, Jeziorski M. Coadministration of MK-801 with amphetamine, cocaine or morphine prevents rather than transiently masks the development of behavioral sensitization. Brain Res 1993;613:291–4.
[226] Weiss SR, Post RM, Pert A, Woodward R, Murman D. Context-dependent cocaine sensitization: differential effect of haloperidol on development versus expression. Pharmacol Biochem Behav 1989;34:655–61.
[227] Wolf ME, Dahlin SL, Hu XT, Xue CJ, White K. Effects of lesions of prefrontal cortex, amygdala, or fornix on behavioral sensitization to amphetamine: comparison with N-methyl-D-aspartate antagonists. Neuroscience 1995;69:417–39.
[228] Kalivas PW, Duffy P. Time course of extracellular dopamine and behavioral sensitization to cocaine. I. Dopamine axon terminals. J Neurosci 1993;13:266–75.
[229] Bradberry CW. Acute and chronic dopamine dynamics in a nonhuman primate model of recreational cocaine use. J Neurosci 2000;20:7109–15.
[230] Ellison G. Stimulant-induced psychosis, the dopamine theory of schizophrenia, and the habenula.. Brain Res Brain Res Rev 1994;19:223–39.
[231] Schlemmer RF, Young J, Davis JM. Stimulant-induced disruption of nonhuman primate social behavior and the psychopharmacology of schizophrenia. J Psychopharmacol 1996;10:64–76.
[232] Castner SA, Goldman-Rakic PS. Long-lasting psychotomimetic consequences of repeated low-dose amphetamine exposure in rhesus monkeys. Neuropsychopharmacology 1999;20:10–28.
[233] Strakowski SM, Sax KW, Setters MJ, Keck Jr PE. Enhanced response to repeated d-amphetamine challenge: evidence for behavioral sensitization in humans. Biol Psychiatry 1996;40:872–80.
[234] Strakowski SM, Sax KW. Progressive behavioral response to repeated d-amphetamine challenge: further evidence for sensitization in humans. Biol Psychiatry 1998;44: 1171–7.
[235] Strakowski SM, Sax KW, Rosenberg HL, DelBello MP, Adler CM. Human response to repeated low-dose d-amphetamine: evidence for behavioral enhancement and tolerance. Neuropsychopharmacology 2001;25:548–54.
[236] Gorelick DA, Rothman RB. Stimulant sensitization in humans. Biol Psychiatry 1997;42:230–1.
[237] Walsh SL, Haberny KA, Bigelow GE. Modulation of intravenous cocaine effects by chronic oral cocaine in humans. Psychopharmacology (Berlin) 2000;150:361–73.
[238] Wachtel SR, de Wit H. Subjective and behavioral effects of repeated d-amphetamine in humans. Behav Pharmacol 1999;10:271–81.
[239] Comer SD, Hart CL, Ward AS, Haney M, Foltin RW, Fischman MW. Effects of repeated oral methamphetamine administration in humans. Psychopharmacology (Berlin) 2001;155:397–404.
[240] Strakowski SM, Sax KW, Setters MJ, Stanton SP, Keck Jr PE. Lack of enhanced response to repeated d-amphetamine challenge in first-episode psychosis: implications for a sensitization model of psychosis in humans. Biol Psychiatry 1997;42:749–55.
[241] Carlezon Jr WA, Konradi C. Understanding the neurobiological consequences of early exposure to psychotropic drugs: linking behavior with molecules. Neuropharmacology 2004;47(Suppl. 1):47–60.
[242] Kalivas PW, Duffy P, DuMars LA, Skinner C. Behavioral and neurochemical effects of acute and daily cocaine administration in rats. J Pharmacol Exp Ther 1988;245: 485–91.
[243] Kuczenski R, Segal DS. Locomotor effects of acute and repeated threshold doses of amphetamine and

methylphenidate: relative roles of dopamine and norepinephrine. J Pharmacol Exp Ther 2001;296:876–83.
[244] Kalivas PW, Stewart J. Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res Rev 1991;16: 223–44.
[245] Piazza PV, Deminiere JM, Le Moal M, Simon H. Factors that predict individual vulnerability to amphetamine self-administration. Science 1989;245:1511–3.
[246] Horger BA, Giles MK, Schenk S. Preexposure to amphetamine and nicotine predisposes rats to self-administer a low dose of cocaine. Psychopharmacology (Berlin) 1992;107:271–6.
[247] Vezina P, Pierre PJ, Lorrain DS. The effect of previous exposure to amphetamine on drug-induced locomotion and self-administration of a low dose of the drug. Psychopharmacology (Berlin) 1999;147:125–34.
[248] Morgan D, Roberts DC. Sensitization to the reinforcing effects of cocaine following binge-abstinent self-administration. Neurosci Biobehav Rev 2004;27:803–12.
[249] Vanderschuren LJ, Kalivas PW. Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. Psychopharmacology (Berlin) 2000;151:99–120.
[250] Nestler EJ. Molecular neurobiology of addiction. Am J Addict 2001;10:201–17.
[251] Robinson TE, Berridge KC. Incentive-sensitization and addiction. Addiction 2001;96:103–14.
[252] Clure C, Brady KT, Saladin ME, Johnson D, Waid R, Rittenbury M. Attention-deficit/hyperactivity disorder and substance use: symptom pattern and drug choice. Am J Drug Alcohol Abuse 1999;25:441–8.
[253] Biederman J, Wilens T, Mick E, Spencer T, Faraone SV. Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk for substance use disorder. Pediatrics 1999;104:e20.
[254] Wilens TE, Faraone SV, Biederman J, Gunawardene S. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics 2003;111:179–85.
[255] Pilotte NS, Sharpe LG, Kuhar MJ. Withdrawal of repeated intravenous infusions of cocaine persistently reduces binding to dopamine transporters in the nucleus accumbens of Lewis rats. J Pharmacol Exp Ther 1994;269:963–9.
[256] Wilson JM, Nobrega JN, Corrigall WA, Coen KM, Shannak K, Kish SJ. Amygdala dopamine levels are markedly elevated after self- but not passive-administration of cocaine. Brain Res 1994;668:39–45.
[257] Claye LH, Akunne HC, Davis MD, DeMattos S, Soliman KFA. Behavioral and neurochemical changes in the dopaminergic system after repeated cocaine administration. Mol Neurobiol 1995;11:55–66.
[258] Boulay D, Duterte-Boucher D, Leroux-Nicollet I, Naudon L, Costenin J. Locomotor sensitization and decrease in [3H]mazindol binding to the dopamine transporter in the nucleus accumbens are delayed after chronic treatments by GBR12782 or cocaine. J Pharmacol Exp Ther 1996;278:330–7.
[259] Tella SR, Ladenheim B, Andrews AM, Goldberg SR, Cadet JL. Differential reinforcing effects of cocaine and GBR-12909: biochemical evidence for divergent neuroadaptive changes in the mesolimbic dopaminergic system. J Neurosci 1996;16:7416–27.
[260] Letchworth SR, Daunais JB, Hedgecock AA, Porrino LJ. Effects of chronic cocaine administration on dopamine transporter mRNA and protein in the rat.. Brain Res 1997;750:214–22.
[261] Letchworth SR, Sexton T, Childers SR, Vrana KE, Vaughan RA, Davies HML, et al. Regulation of rat dopamine transporter mRNA and protein by chronic cocaine administration. J Neurochem 1999;73:1982–9.
[262] Goeders NE, Kuhar MJ. Chronic cocaine administration induces opposite changes in dopamine receptors in the striatum and nucleus accumbens. Alcohol Drug Res 1987;7:207–16.
[263] Dwoskin LP, Peris J, Yasuda RP, Philpott K, Zahniser NR. Repeated cocaine administration results in supersensitivity of striatal D-2 dopamine autoreceptors to pergolide. Life Sci 1988;42:255–62.
[264] Kleven MS, Perry BD, Woolverton WL, Seiden LS. Effects of repeated injections of cocaine on D1 and D2 dopamine receptors in rat brain. Brain Res 1990;532:265–70.
[265] Kuhar MJ, Pilotte NS. Neurochemical changes in cocaine withdrawal. Trends Pharmacol Sci 1996;17:260–4.
[266] Anderson SM, Pierce RC. Cocaine-induced alterations in dopamine receptor signaling: implications for reinforcement and reinstatement. Pharmacol Ther 2005;106:389–403.
[267] Mateo Y, Lack CM, Morgan D, Roberts DC, Jones SR. Reduced dopamine terminal function and insensitivity to cocaine following cocaine binge self-administration and deprivation. Neuropsychopharmacology 2005;30:1455–63.
[268] Letchworth SR, Nader MA, Smith HR, Friedman DP, Porrino LJ. Progression of changes in dopamine transporter binding site density as a result of cocaine self-administration in rhesus monkeys. J Neurosci 2001;21:2799–807.
[269] Little KY, Kirkman JA, Carroll FI, Clark TB, Duncan GE. Cocaine use increases [3H]WIN 35428 binding sites in human striatum. Brain Res 1993;628:17–25.
[270] Staley JK, Hearn WL, Ruttenber AJ, Wetli CV, Mash DC. High affinity cocaine recognition sites on the dopamine transporter are elevated in fatal cocaine overdose victims. J Pharmacol Exp Ther 1994;271:1678–85.
[271] Moore RJ, Vinsant SL, Nader MA, Porrino LJ, Friedman DP. Effect of cocaine self-administration on striatal dopamine D1 receptors in rhesus monkeys. Synapse 1998;28:1–9.
[272] Nader MA, Daunais JB, Moore T, Nader SH, Moore RJ, Smith HR, et al. Effects of cocaine self-administration on striatal dopamine systems in rhesus monkeys. Initial and chronic exposure. Neuropsychopharmacology 2002;27:35–46.
[273] Moore RJ, Vinsant SL, Nader MA, Porrino LJ, Friedman DP. Effect of cocaine self-administration on dopamine D2 receptors in rhesus monkeys. Synapse 1998;30:88–96.
[274] Nader MA, Morgan D, Gage HD, Nader SH, Calhoun TL, Buchheimer N, et al. PET imaging of dopamine D2 receptors during chronic cocaine self-administration in monkeys. Nat Neurosci 2006;9:1050–6.
[275] Martinez D, Narendran R, Foltin RW, Slifstein M, Hwang DR, Broft A, et al. Amphetamine-induced dopamine release: markedly blunted in cocaine dependence and predictive of the choice to self-administer cocaine. Am J Psychiatry 2007;164:622–9.
[276] Garavan H, Pankiewicz J, Bloom A, Cho JK, Sperry L, Ross TJ, et al. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. Am J Psychiatry 2000;157:1789–98.
[277] Martin-Soelch C, Leenders KL, Chevalley AF, Missimer J, Kunig G, Magyar S, et al. Reward mechanisms in the brain and their role in dependence: evidence from neurophysiological and neuroimaging studies. Brain Res Brain Res Rev 2001;36:139–49.
[278] Malison RT, Best SE, van Dyck CH, McCance EF, Wallace EA, Laruelle M, et al. Elevated striatal dopamine

transporters during acute cocaine abstinence as measured by [123I] beta-CIT SPECT. Am J Psychiatry 1998;155:832–4.
[279] Volkow ND, Fowler JS. Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. Cereb Cortex 2000;10:318–25.
[280] Volkow ND, Fowler JS, Wang GJ. The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. Neuropharmacology 2004;47(Suppl. 1):3–13.
[281] Volkow ND, Fowler JS, Wang GJ, Hitzemann R, Logan J, Schlyer DJ, et al. Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. Synapse 1993;14:169–77.
[282] Volkow ND, Chang L, Wang GJ, Fowler JS, Ding YS, Sedler M, et al. Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. Am J Psychiatry 2001;158: 2015–21.
[283] Volkow ND, Fowler JS, Wolf AP, Hitzemann R, Dewey S, Bendriem B, et al. Changes in brain glucose metabolism in cocaine dependence and withdrawal. Am J Psychiatry 1991;148:621–6.
[284] Volkow ND, Wang GJ, Fowler JS, Gatley SJ, Logan J, Ding YS, et al. Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. Am J Psychiatry 1998;155:1325–31.
[285] Volkow ND, Wang G, Fowler JS, Logan J, Gerasimov M, Maynard L, et al. Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. J Neurosci 2001;21:RC121.
[286] Laruelle M. Imaging synaptic neurotransmission with in vivo binding competition techniques: a critical review. J Cereb Blood Flow Metab 2000;20:423–51.
[287] Vaidya CJ, Austin G, Kirkorian G, Ridlehuber HW, Desmond JE, Glover GH, et al. Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. Proc Natl Acad Sci USA 1998;95:14494–9.
[288] Schweitzer JB, Lee DO, Hanford RB, Tagamets MA, Hoffman JM, Grafton ST, et al. A positron emission tomography study of methylphenidate in adults with ADHD: alterations in resting blood flow and predicting treatment response. Neuropsychopharmacology 2003;28:967–73.
[289] Ernst M, Zametkin AJ, Matochik JA, Liebenauer L, Fitzgerald GA, Cohen RM. Effects of intravenous dextroamphetamine on brain metabolism in adults with attention-deficit hyperactivity disorder (ADHD). Preliminary findings. Psychopharmacol Bull 1994;30: 219–25.
[290] Matochik JA, Liebenauer LL, King AC, Szymanski HV, Cohen RM, Zametkin AJ. Cerebral glucose metabolism in adults with attention deficit hyperactivity disorder after chronic stimulant treatment. Am J Psychiatry 1994;151:658–64.
[291] Baumann MH, Rothman RB. Alterations in serotonergic responsiveness during cocaine withdrawal in rats: similarities to major depression in humans. Biol Psychiatry 1998;44:578–91.
[292] Cunningham KA, Bradberry CW, Chang AS, Reith ME. The role of serotonin in the actions of psychostimulants: molecular and pharmacological analyses. Behav Brain Res 1996;73:93–102.
[293] Parsons LH, Koob GF, Weiss F. Serotonin dysfunction in the nucleus accumbens of rats during withdrawal after unlimited access to intravenous cocaine. J Pharmacol Exp Ther 1995;274:1182–91.
[294] Pierce RC, Kalivas PW. A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants. Brain Res Brain Res Rev 1997;25: 192–216.
[295] Egan MF, Wing L, Li R, Kirch DG, Wyatt RJ. Effects of chronic cocaine treatment on rat brain: long-term reduction in frontal cortical serotonin. Biol Psychiatry 1994;36:637–40.
[296] Little KY, Patel UN, Clark TB, Butts JD. Alteration of brain dopamine and serotonin levels in cocaine users: a preliminary report. Am J Psychiatry 1996;153:1216–8.
[297] Banks ML, Czoty PW, Gage HD, Bounds MC, Garg PK, Garg S, et al. Effects of cocaine and MDMA self-administration on serotonin transporter availability in monkeys. Neuropsychopharmacology 2008;33:219–25.
[298] McDougle CJ, Black JE, Malison RT, Zimmermann RC, Kosten TR, Heninger GR, et al. Noradrenergic dysregulation during discontinuation of cocaine use in addicts. Arch Gen Psychiatry 1994;51:713–9.
[299] Macey DJ, Smith HR, Nader MA, Porrino LJ. Chronic cocaine self-administration upregulates the norepinephrine transporter and alters functional activity in the bed nucleus of the stria terminalis of the rhesus monkey. J Neurosci 2003;23:12–6.
[300] Mash DC, Ouyang Q, Qin Y, Pablo J. Norepinephrine transporter immunoblotting and radioligand binding in cocaine abusers. J Neurosci Methods 2005;143: 79–85.
[301] Reid MS, Berger SP. Evidence for sensitization of cocaine-induced nucleus accumbens glutamate release. Neuroreport 1996;7:1325–9.
[302] Swanson CJ, Baker DA, Carson D, Worley PF, Kalivas PW. Repeated cocaine administration attenuates group I metabotropic glutamate receptor-mediated glutamate release and behavioral activation: a potential role for Homer. J Neurosci 2001;21:9043–52.
[303] Thomas MJ, Beurrier C, Bonci A, Malenka RC. Long-term depression in the nucleus accumbens: a neural correlate of behavioral sensitization to cocaine. Nat Neurosci 2001;4:1217–23.
[304] Beurrier C, Malenka RC. Enhanced inhibition of synaptic transmission by dopamine in the nucleus accumbens during behavioral sensitization to cocaine. J Neurosci 2002;22:5817–22.
[305] Dole VP, Nyswander M. A medical treatment for diacetylmorphine (heroin) addiction. A clinical trial with methadone hydrochloride. J Am Med Assoc 1965;193: 646–50.
[306] Kreek MJ. Rationale for maintenance pharmacotherapy of opiate dependence. Res Publ Assoc Res Nerv Ment Dis 1992;70:205–30.
[307] Rose JE, Behm FM, Westman EC. Nicotine-mecamylamine treatment for smoking cessation: the role of pre-cessation therapy. Exp Clin Psychopharmacol 1998;6:331–43.
[308] O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence. A controlled study. Arch Gen Psychiatry 1992;49:881–7.
[309] Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry 1992;49:876–80.
[310] Grabowski J, Shearer J, Merrill J, Negus SS. Agonist-like, replacement pharmacotherapy for stimulant abuse and dependence. Addict Behav 2004;29:1439–64.
[311] Sofuoglu M, Kosten TR. Novel approaches to the treatment of cocaine addiction. CNS Drugs 2005;19:13–25.
[312] Gorelick DA. Pharmacological intervention for cocaine, crack, and other stimulant addiction. In: Graham AW, Schultz TK, Mayo-Smith MF, Ries RK, Wilford BB, editors. Principles of addiction medicine. Chevy Chase, MD: American Society of Addiction Medicine; 2003. p. 785–800.

[313] de Lima MS, de Oliveira Soares BG, Reisser AA, Farrell M. Pharmacological treatment of cocaine dependence: a systematic review. Addiction 2002;97:931–49.
[314] Soares BG, Lima MS, Reisser AA, Farrell M. Dopamine agonists for cocaine dependence. Cochrane Database Syst Rev 2003:CD003352.
[315] Grabowski J, Rhoades H, Silverman P, Schmitz JM, Stotts A, Creson D, et al. Risperidone for the treatment of cocaine dependence: randomized, double-blind trial. J Clin Psychopharmacol 2000;20:305–10.
[316] Evans SM, Walsh SL, Levin FR, Foltin RW, Fischman MW, Bigelow GE. Effect of flupenthixol on subjective and cardiovascular responses to intravenous cocaine in humans. Drug Alcohol Depend 2001;64:271–83.
[317] Kampman KM, Pettinati H, Lynch KG, Sparkman T, O'Brien CP. A pilot trial of olanzapine for the treatment of cocaine dependence. Drug Alcohol Depend 2003;70: 265–73.
[318] George TP, Verrico CD, Picciotto MR, Roth RH. Nicotinic modulation of mesoprefrontal dopamine neurons: pharmacologic and neuroanatomic characterization. J Pharmacol Exp Ther 2000;295:58–66.
[319] Petrakis IL, Carroll KM, Nich C, Gordon LT, McCance-Katz EF, Frankforter T, et al. Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts. Addiction 2000;95:219–28.
[320] Carroll KM, Fenton LR, Ball SA, Nich C, Frankforter TL, Shi J, et al. Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. Arch Gen Psychiatry 2004;61: 264–72.
[321] Levin FR, Lehman AF. Meta-analysis of desipramine as an adjunct in the treatment of cocaine addiction. J Clin Psychopharmacol 1991;11:374–8.
[322] Arndt IO, Dorozynsky L, Woody GE, McLellan AT, O'Brien CP. Desipramine treatment of cocaine dependence in methadone-maintained patients. Arch Gen Psychiatry 1992;49:888–93.
[323] Campbell JL, Thomas HM, Gabrielli W, Liskow BI, Powell BJ. Impact of desipramine or carbamazepine on patient retention in outpatient cocaine treatment: preliminary findings. J Addict Dis 1994;13:191–9.
[324] Kosten TR, Morgan CM, Falcione J, Schottenfeld RS. Pharmacotherapy for cocaine-abusing methadone-maintained patients using amantadine or desipramine. Arch Gen Psychiatry 1992;49:894–8.
[325] Walsh SL, Preston KL, Sullivan JT, Fromme R, Bigelow GE. Fluoxetine alters the effects of intravenous cocaine in humans. J Clin Psychopharmacol 1994;14:396–407.
[326] Batki SL, Washburn AM, Delucchi K, Jones RT. A controlled trial of fluoxetine in crack cocaine dependence. Drug Alcohol Depend 1996;41:137–42.
[327] Grabowski J, Rhoades H, Elk R, Schmitz J, Davis C, Creson D, et al. Fluoxetine is ineffective for treatment of cocaine dependence or concurrent opiate and cocaine dependence: two placebo-controlled double-blind trials. J Clin Psychopharmacol 1995;15:163–74.
[328] Hollister LE, Krajewski K, Rustin T, Gillespie H. Drugs for cocaine dependence: not easy. Arch Gen Psychiatry 1992;49:905–6.
[329] Specker S, Crosby R, Borden J, Hatsukami D. Nefadozone in the treatment of females with cocaine abuse. Drug Alcohol Depend 2000;60:S211.
[330] Platt DM, Rowlett JK, Spealman RD. Modulation of cocaine and food self-administration by low- and high-efficacy d1 agonists in squirrel monkeys. Psychopharmacology (Berlin) 2001;157:208–16.
[331] Mutschler NH, Bergman J. Effects of chronic administration of the D(1) receptor partial agonist SKF 77434 on cocaine self-administration in rhesus monkeys. Psychopharmacology (Berlin) 2002;160:362–70.
[332] Platt DM, Rodefer JS, Rowlett JK, Spealman RD. Suppression of cocaine- and food-maintained behavior by the D2-like receptor partial agonist terguride in squirrel monkeys. Psychopharmacology (Berlin) 2003;166:298–305.
[333] Kumor K, Sherer M, Jaffe J. Effects of bromocriptine pretreatment on subjective and physiological responses to i.v. cocaine. Pharmacol Biochem Behav 1989;33:829–37.
[334] Montoya ID, Preston KL, Rothman R, Gorelick DA. Open-label pilot study of bupropion plus bromocriptine for treatment of cocaine dependence. Am J Drug Alcohol Abuse 2002;28:189–96.
[335] Preston K, Sullivan JT, Strain EC, Bigelow GE. Effects of cocaine alone and in combination with mazindol in human cocaine abusers. J Pharmacol Exp Ther 1993;267:296–307.
[336] Stine SM, Krystal JH, Kosten TR, Charney DS. Mazindol treatment for cocaine dependence. Drug Alcohol Depend 1995;39:245–52.
[337] Grabowski J, Roache JD, Schmitz JM, Rhoades H, Creson D, Korszun A. Replacement medication for cocaine dependence: methylphenidate. J Clin Psychopharmacol 1997;17:485–8.
[338] Schubiner H, Saules KK, Arfken CL, Johanson CE, Schuster CR, Lockhart N, et al. Double-blind placebo-controlled trial of methylphenidate in the treatment of adult ADHD patients with comorbid cocaine dependence. Exp Clin Psychopharmacol 2002;10:286–94.
[339] Howell LL, Wilcox KM. The dopamine transporter and cocaine medication development: drug self-administration in nonhuman primates. J Pharmacol Exp Ther 2001;298:1–6.
[340] Negus SS. Rapid assessment of choice between cocaine and food in rhesus monkeys: effects of environmental manipulations and treatment with d-amphetamine and flupenthixol. Neuropsychopharmacology 2003;28: 919–31.
[341] Negus SS, Mello NK. Effects of chronic d-amphetamine treatment on cocaine- and food-maintained responding under a second-order schedule in rhesus monkeys. Drug Alcohol Depend 2003;70:39–52.
[342] Rothman RB, Blough BE, Woolverton WL, Anderson KG, Negus SS, Mello NK, et al. Development of a rationally designed, low abuse potential, biogenic amine releaser that suppresses cocaine self-administration. J Pharmacol Exp Ther 2005;313:1361–9.
[343] Glowa JR, Wojnicki FHE, Matecka D, Bacher JJ, Mansbach RS, Balster RL, et al. Effects of dopamine reuptake inhibitors on food- and cocaine-maintained responding. I. Dependence on unit dose of cocaine. Exp Clin Psychopharmacol 1995;3:219–31.
[344] Dackis C, O'Brien C. Glutamatergic agents for cocaine dependence. Ann NY Acad Sci 2003;1003:328–45.
[345] Touret M, Sallanon-Moulin M, Fages C, Roudier V, Didier-Bazes M, Roussel B, et al. Effects of modafinil-induced wakefulness on glutamine synthetase regulation in the rat brain. Brain Res Mol Brain Res 1994;26:123–8.
[346] Dackis CA, Lynch KG, Yu E, Samaha FF, Kampman KM, Cornish JW, et al. Modafinil and cocaine: a double-blind, placebo-controlled drug interaction study. Drug Alcohol Depend 2003;70:29–37.
[347] Dackis CA, Kampman KM, Lynch KG, Pettinati HM, O'Brien CP. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. Neuropsychopharmacology 2005;30:205–11.
[348] Mignot E, Nishino S, Guilleminault C, Dement WC. Modafinil binds to the dopamine uptake carrier site with low affinity. Sleep 1994;17:436–7.

[349] Dopheide MM, Morgan RE, Rodvelt KR, Schachtman TR, Miller DK. Modafinil evokes striatal [(3)H]dopamine release and alters the subjective properties of stimulants. Eur J Pharmacol 2007;568:112–23.
[350] Wisor JP, Nishino S, Sora I, Uhl GH, Mignot E, Edgar DM. Dopaminergic role in stimulant-induced wakefulness. J Neurosci 2001;21:1787–94.
[351] Vocci F, Ling W. Medications development: successes and challenges. Pharmacol Ther 2005;108:94–108.
[352] Shoptaw S, Yang X, Rotheram-Fuller EJ, Hsieh YC, Kintaudi PC, Charuvastra VC, et al. Randomized placebo-controlled trial of baclofen for cocaine dependence: preliminary effects for individuals with chronic patterns of cocaine use. J Clin Psychiatry 2003;64:1440–8.
[353] Gonzalez G, Sevarino K, Sofuoglu M, Poling J, Oliveto A, Gonsai K, et al. Tiagabine increases cocaine-free urines in cocaine-dependent methadone-treated patients: results of a randomized pilot study. Addiction 2003;98:1625–32.
[354] Shank RP, Gardocki JF, Streeter AJ, Maryanoff BE. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. Epilepsia 2000;41(Suppl. 1): S3–9.
[355] Kampman KM, Pettinati H, Lynch KG, Dackis C, Sparkman T, Weigley C, et al. A pilot trial of topiramate for the treatment of cocaine dependence. Drug Alcohol Depend 2004;75:233–40.