Monoamine transporters and psychostimulant addiction

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A B S T R A C T

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.

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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...
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 neurotransmitter 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>
<thead>
<tr>
<th>Drug</th>
<th>Trade names</th>
<th>Medical indications</th>
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<tbody>
<tr>
<td>Amphetamine</td>
<td>Adderall®</td>
<td>ADHD, narcolepsy, weight control</td>
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<tr>
<td></td>
<td>Dextrostat®</td>
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<td></td>
<td>Dextedrine®</td>
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<tr>
<td>Diethylpropion</td>
<td>Tenuate®</td>
<td>Weight control</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Adipex®</td>
<td>ADHD, weight control</td>
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<td></td>
<td>Desoxyn®</td>
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<td></td>
<td>Methedrine®</td>
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<tr>
<td>Methylphenidate</td>
<td>Ritalin®</td>
<td>ADHD, narcolepsy</td>
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<tr>
<td>Phentermine</td>
<td>Adipex-P®</td>
<td>Weight control</td>
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<td>Fastin®</td>
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<td></td>
<td>Ionamin®</td>
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Table 1 - Examples of psychostimulants used as therapeutics in the United States
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 contribute 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 homooligmeric 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 terminals, 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 dys-function 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.
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 D1-like (D1 and D5 receptors) and D2-like (D2, D3, and D4 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dopamine IC₅₀ (nM)</th>
<th>Serotonin IC₅₀ (nM)</th>
<th>Norepinephrine IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-) Cocaine</td>
<td>478⁺</td>
<td>304⁺</td>
<td>779⁺</td>
</tr>
<tr>
<td>(+) Amphetamine</td>
<td>34⁺</td>
<td>3830⁻</td>
<td>39⁻</td>
</tr>
<tr>
<td>(+) Methamphetamine</td>
<td>114⁻</td>
<td>2137⁺</td>
<td>48⁺</td>
</tr>
<tr>
<td>(+) Methylphenidate</td>
<td>82⁺</td>
<td>7600⁻</td>
<td>440⁻</td>
</tr>
</tbody>
</table>

Table 2 – Drug affinities at monoamine transporters.

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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 [3H]cocaine in the caudate and the ability of those compounds to produce cocaine-like behavioral effects in squirrel monkeys [116–118]. Dopamine and cocaine-selective 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 5HT2C 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 5HT2C agonists [158], resulting in a decrease in nucleus accumbens dopamine levels [159]. Conversely, selective serotonin 5HT2C antagonists increase the activity of these neurons [160], leading to increased dopamine release in the nucleus accumbens [161]. Since serotonin 5HT2C receptors appear to be located exclusively on GABA neurons [162], the effects of serotonin 5HT2C receptor stimulation are likely to be indirectly mediated by an enhancement of GABA-mediated inhibition of VTA dopamine neurons. Localization of serotonin 5HT2C 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_{1A} receptors can enhance cocaine reinforcement [166], likely by decreasing GABA-mediated inhibition in the VTA [163]. Serotonin 5HT_{2} 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 \( \alpha_1 \)-adrenoceptor 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 \( \alpha_1 \)-adrenoceptors can also attenuate amphetamine- and cocaine-induced locomotion and sensitization in rodents [175–177]. Similarly, \( \alpha_2 \)-adrenoceptor 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 \( \alpha_1 \)-adrenoceptor mechanisms in the discriminative-stimulus effects of cocaine [179]. Moreover, the \( \alpha_2 \)-adrenoceptor 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\(_A\) 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 D1-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 block 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 neuropsychopharmacology 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 D1- or D2-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 D1 and D2 dopamine receptors [266]. The equivocal results likely reflect different dosing regimens and withdrawal periods, as well as the use of non-contingent 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 post-mortem 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 D2 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 D2 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, D2-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 [11C]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 D3 receptors have reliably documented long-lasting decreases in D3-receptor density in stimulant abusers [279]. The reduction in D3-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 D3 receptors [281,282]. Reductions in striatal D3 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-HT1A 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 \(\alpha\)-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 methylenidate. 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]. Antagonist 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 D2-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 D2/D3-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 D2-like receptor agonist and a partial D1-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-administration 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_A 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


[34] Foster JD, Panansorn B, Vaughan RA. Dopamine transporters are phosphorylated on N-terminal serines in rat striatum. J Biol Chem 2002;277:25178–86.


[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.


