CNS STIMULANTS

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1. INTRODUCTION

Natural products that have stimulant properties have been known for millennia, and their active species (including ephedrine and cocaine) are now well known. Central nervous system (CNS) Stimulants, also called psychostimulants, are drugs that lead to increased arousal, improved performance on tasks of vigilance and alertness, and a sense of self-confidence and well being. High doses can produce feelings of elation or euphoria and because of these effects stimulants have reinforcing properties, and can produce dependence. That is, because they make users feel “good,” they are sometimes taken for extended periods of time in an attempt to maintain an elevated mood. Tolerance develops to the mood elevating properties of psychostimulants, however, and more and more of the drug must be taken to maintain the effect. Increased doses also prevent sleep, and continued use can result in symptoms of psychosis. Cessation of the drug after one of these binges (abstinence) may lead to an emotional and physical “crash” (the result of poor nutrition, lack of sleep, and increased physical activity), and severely depressed mood. In dependent individuals, intense craving for the drug occurs, resulting in another period of drug seeking, extensive drug use, and subsequent crash. This cycle is repeated in chronic psychostimulant dependence.

The reader should be aware that in this chapter the use of the term “CNS stimulation” encompasses several physiological mechanisms of action, and many different types of biologically active substances. A number of different agents, such as caffeine, affect these pharmacological mechanisms and cause CNS stimulation. Other diverse examples include strychnine (causing CNS stimulants by blockade of inhibitory glycine receptors), and benzodiazepine inverse agonists (causing CNS stimulation by attenuating the inhibitory effects of GABA on chloride channels). It is not the intent of this chapter to provide an encyclopedic treatment of all the possible substances that can cause “CNS stimulation,” but rather to focus primarily on the psychostimulants (i.e., drugs that affect brain monoaminergic systems).

Many CNS stimulants also have appetite suppressant effects that led to their use in treating obesity. In short-term studies, amphetamine-like drugs have been shown to be more effective than placebo in promoting weight loss. Long-term (>20 weeks) weight loss has not been shown, however, unless the drug is taken continuously [1]. At one time, stimulants were widely prescribed for appetite control, but they lose efficacy rather quickly through the development of tolerance. Thus, it was not uncommon for patients to become dependent on them, with symptoms of withdrawal upon abrupt cessation. The increased awareness of the addictive potential of stimulants, coupled with their widespread abuse, has led to much more extensive restrictions over their availability. These drugs are much more carefully controlled today, and are rarely used for weight control except in a few special instances.

There remain some important medical uses for this class of drug, yet as noted later, the therapeutic actions of psychostimulants must be balanced against their undesirable actions. Issues of dependence, tolerance, and potential abuse must be considered when deciding whether treatment with a psychostimulant is an appropriate therapy. Nonetheless, new generations of drugs that have sprung from an understanding of the classic stimulants may open important therapeutic horizons for the future.

1.1. Ephedra and Khat

The Chinese drug ma huang (Ephedra sinica Stapf) has been used in China for more than 5000 years. The alkaloid that is responsible for the CNS stimulant effects is ephedrine. The levorotatory erythro isomer (I) is the most active of the four possible stereoisomers with that structural formula. Khat (kat, or qat) or Abyssinian tea (Catha edulis Forskal)
is the product from a small tree or shrub indigenous to tropical East Africa. Khat leaves are chewed habitually by peoples in East Africa and certain other Arabian countries, and produce a mild CNS stimulant effect [2]. The principle active component in Khat is a substituted phenethylamine derivative known as (−)-cathinone 2 [3].

Both of these compounds possess a beta-phenethylamine framework, a common structural theme that occurs in many related CNS stimulants. In general, these compounds have similar mechanisms of action.

(−)-Cocaine 3 has a completely different structure, and as we shall see later, its mechanism of action is also somewhat different from the structurally simpler 1 and 2. Nevertheless, all of these natural prototype CNS stimulants have the common action of exerting powerful effects on brain pathways that utilize dopamine as the neurotransmitter.

1.2. Caffeine

From an economic standpoint, the most important central nervous system stimulant is caffeine, 1,3,7-trimethylxanthine 4. It occurs naturally and is a product of kola (cola) nuts (Cola nitida, where it occurs to the extent of approximately 3.5%, by weight), of coffee beans (Coffea arabica where it comprises approximately 1–2% by weight), and tea (Camellia sinensis where it makes up 1–4% of the mass of dried leaves). The annual consumption of caffeine has been estimated at 120 million kilograms, the approximate equivalent of one caffeine-containing beverage per day for each of the world’s five billion plus inhabitants. As a beverage, the worldwide consumption of tea is surpassed only by water. The structurally related dimethylxanthines theophylline 5 and theobromine 6 have less of a CNS stimulant effect, and are principally important for their ability to relax smooth muscle. Cocoa and chocolate have little caffeine, but do contain theobromine.

A regular cup of coffee contains between 40 and 176 mg of caffeine, with a mean content of approximately 85 mg. Tea contains less caffeine, with an average of approximately 27 mg per cup, and an ounce of sweet chocolate typically contains between 75 and 150 mg of combined methylxanthines [4]. Caffeinated “energy drinks” are increasing dramatically in popularity, and these can contain anywhere from 75 to 505 mg of caffeine, depending on the brand [5].

2. HISTORY

The historical development of amphetamine and methamphetamine is described in interesting detail by Angrist and Sudilovsky [6]. The discovery of psychostimulants differs somewhat from the usual drug discovery process because there was a long folkloric history of use of khat, coca leaves, and ma huang.
(ephedra). Although there may not have been a formal pharmacological classification of CNS stimulants at that time, the ability of these agents to alleviate fatigue was certainly well recognized.

Amphetamine itself was first synthesized in 1887 and studied as early as 1910, but its stimulant effects were not discovered for another approximately 20 years. Amphetamine was independently resynthesized in 1927 by the noted psychopharmacologist Gordon Alles in a program to develop synthetic substitutes for ephedrine, a drug then being used as a bronchodilator for the treatment of asthma [7]. The central stimulant effects of amphetamine were probably noted about 1930, when it appeared in nasal inhalers in Germany. The first medical use for amphetamine was in the treatment of narcolepsy [8] and by 1936 orally active Benzedrine tablets were available without prescription [9]. By 1937, it was being used recreationally by the general population, with particular popularity among American college students [10].

It is not clear when or by whom methamphetamine was first synthesized. Various accounts indicate its first preparation somewhere between 1888 and 1934 [6]. In any case, Hauschild [11] published the first studies of the pharmacology of methamphetamine in 1938, characterized its stimulant effects in animals, and also carried out a self-experiment.

3. CLINICAL USE OF AGENTS

3.1. Therapeutic Applications

Psychostimulants generally increase the level of activity, alleviate fatigue, increase alertness, and elevate mood (or cause euphoria in high doses). Unfortunately, the ability to produce euphoria leads these compounds to have a high potential for abuse and dependence. The principal clinical indications for psychostimulants are in the treatment of attention deficit hyperactivity disorder (ADHD) and the sleep disorder known as narcolepsy. A less commonly recognized use, but one that is gaining importance, is in the treatment of depression in terminal patients or the chronically ill [12–14]. There also is need for psychostimulants in certain occupations, for example, in the military, as a countermeasure to fatigue from irregular or prolonged work hours, where a high level of vigilance and alertness must be maintained [15,16]. Some specific clinical applications will now be discussed.

Attention deficit hyperactivity disorder is a diagnosis applied mostly to children, but one that persists into adulthood for many people. It is reflected in a persistent pattern of inattention and/or hyperactivity–impulsivity that is more frequent and severe than typically observed in individuals at a comparable level of development [17]. Inattention prevents ADHD patients from keeping their mind on one thing and focusing their attention; they are easily bored with a task after only a short while. They have no difficulty devoting attention to activities they enjoy, but find it hard to focus conscious attention to organizing or completing a task, or learning something new. They may forget to plan ahead and tasks are rarely completed, or are filled with errors.

Children with ADHD (particularly of school age) have great difficulty being still, they may be in and out of their seats, and talk incessantly. The inability to focus makes learning tasks boring, and exacerbates the desire to move around and become involved in distractions. ADHD children may squat, shake their legs, touch everything, or make distracting noises. Hyperactive teens and adults may feel intensely restless, and may try to do several things at once, going from one activity to the next. Impulsivity is another characteristic of ADHD, with patients often acting without thinking about the consequences. They may have difficulty curbing their immediate reactions to situations, making inappropriate remarks without thinking what they are saying. They find it hard to wait for things they want or to wait to take their turn.

In normal subjects, psychostimulants can increase activity and talkativeness, especially at higher doses. Paradoxically, in ADHD sufferers, stimulants appear to have a calming effect, and allow an increased focus and attention to tasks. While appearing paradoxical, it is now believed that the decreases
in activity in ADHD are secondary to improvements in attention. This beneficial effect of low doses of the stimulants has led to a large number of children being prescribed methylphenidate (Ritalin®) or various amphetamine preparations for the treatment of ADHD. That, in turn, led to great concern about these drugs being overprescribed for ADHD, and that children who are merely highly energetic were routinely being given them for behavior management. The reader should be aware of this social issue, but it requires no further comment in the context of this chapter.

*Narcolepsy* is a condition that includes as its predominant symptoms excessive daytime sleepiness (EDS), persistent drowsiness, and daytime sleep attacks that may occur without warning and are often irresistible. Another hallmark symptom of narcolepsy is cataplexy, which is a sudden loss of voluntary muscle control, often triggered by emotions such as laughter or surprise. Cataplexy occurs more frequently during stress or fatigue. The attack may involve only a feeling of weakness and limp muscles or it may result in total muscular collapse, during which the person can appear unconscious, but actually remains awake and alert. Attacks may be very brief or may last for tens of minutes. Another characteristic symptom of narcolepsy is hypnagogic hallucinations. These are vivid, realistic, and often frightening, reminiscent of nightmares, and usually accompanied by sleep paralysis, a temporary inability to move. Whereas the psychostimulants can have a beneficial effect, they are likely to be supplanted by newer drugs that are more specific and have fewer side effects.

*Use for depression in terminal illness.* Although this indication for psychostimulants is not as widely recognized, agents such as amphetamine and methylphenidate are preferred because they do not suffer from the weeks-long delay in onset of action that is characteristic of traditional antidepressant medications. Thus, a rapid antidepressant response can be achieved in severely ill patients, who in some cases may not survive the several weeks necessary for a traditional antidepressant medication to begin to have an effect [12,18–20].

*Use in obesity.* As noted earlier, many of the psychostimulants also have been used as anorectics (anorexics; anorexigenics) (Table 1), that is, as appetite suppressants. A few of them are still useful in this regard, but the high abuse potential of psychostimulants, coupled with the development of tolerance to their anorectic effects, has meant that prescribing psychostimulants for weight control has generally fallen into disfavor.

*Apnea in premature infants.* Apnea of prematurity (AOP) occurs in approximately 90% of premature neonates weighing less than 1 kg at birth, and in 25% of infants with a weight of less than 2.5 kg [21]. The first line pharmacological therapies for the management of AOP, to stimulate respiration, are the methylxanthines, with theophylline (5) presently being most extensively used. Recent studies suggest, however, that caffeine (4) should be considered the drug of choice because of similar efficacy, longer half-life, fewer adverse effects, and better brain penetration than theophylline [22].

### 3.2. Side Effects, Adverse Effects, and Drug Interactions

Generally, psychostimulants such as amphetamine (7) and methylphenidate (8) can be used safely with most classes of medications and with few contraindications [23]. The acute adverse reactions to stimulants can generally be understood from the perspective of their pharmacology. Psychostimulants act as indirect sympathomimetic agents; they either directly release stored catecholamines, including those in peripheral adrenergic neurons responsible for vascular tone, or block their reuptake. These actions affect the cardiovascular system in fairly predictable ways. In addition, cocaine produces a local anesthetic effect by the blockade of sodium channels [24]. Although that would normally be the pharmacological basis for a class I antiarrhythmic drug, it paradoxically induces proarrhythmia [25].
<table>
<thead>
<tr>
<th>Generic Name (Structure)</th>
<th>Trade Name</th>
<th>Originator</th>
<th>Chemical Class</th>
<th>Dose (mg/day)</th>
</tr>
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<tbody>
<tr>
<td><strong>Psychostimulants</strong></td>
<td></td>
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<tr>
<td>Cocaine HCl (3)</td>
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<td>Mallinckrodt</td>
<td>Ecgonine methyl ester benzoate</td>
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<td>Shire Richwood</td>
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<td>5–10</td>
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<td>Methamphetamine HCl (11)</td>
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<td>Abbott</td>
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<td>5</td>
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<tr>
<td>Methylphenidate HCl (8)</td>
<td>Methylin</td>
<td>Mallinckrodt</td>
<td>α-Phenyl-2-piperidineacetic acid methyl ester</td>
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<td>Caffeine (4)</td>
<td>Quick Pep; Caffedrine; NoDoz; Stay Awake; Vivarin; Stay Alert; Enerjets; Starbucks</td>
<td>Thompson; Thompson; Bristol-Meyers; Major; SK-Beecham; Apothecary; Chilton</td>
<td>Trimethylxanthine</td>
<td>75–200</td>
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<td><strong>Anorexiants</strong></td>
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<td>Upjohn</td>
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<td>Bontril PDM</td>
<td>Phendimetrazine</td>
<td>Carnrick</td>
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<tr>
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Table 1 (Continued)

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<th>Generic Name (Structure)</th>
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<th>Originator</th>
<th>Chemical Class</th>
<th>Dose (mg/day)</th>
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<td>Ion</td>
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<td>Adipex-P</td>
<td>Lemmon</td>
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<td>Holloway</td>
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<td>50 mg/mL</td>
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*aAdministered orally unless otherwise noted.*
In addition to acute effects, however, prolonged usage of amphetamines (and other psychostimulants) can produce an “amphetamine psychosis.” This syndrome was first clearly documented by Connell [26], and is regarded as very similar to paranoid schizophrenia, comprising “paranoid psychosis with ideas of reference, delusions of persecution, auditory and visual hallucinations in a setting of clear consciousness” [26]. The psychosis clears quickly after the drug is withdrawn. Psychosis has been induced experimentally in normal subjects by continuous amphetamine administration [27]. Amphetamine psychosis has been discussed extensively by Angrist [28]. Interestingly, psychostimulants can induce a psychotogenic response in schizophrenics, in doses that are subpsychotogenic in normal subjects, and methylphenidate was found to have greater potency in that regard [29]. Activation of psychotic symptoms by methylphenidate was found to be a predictor of relapse risk [30]. These, and other similar studies, are all consistent with the dopamine hypothesis of schizophrenia.

**Methylphenidate.** Methylphenidate (Ritalin) is widely prescribed for the treatment of ADHD. Indeed, methylphenidate remains the most common drug therapy for treatment of ADHD [31], and approximately 90% of children treated for ADHD are given this drug [32], representing approximately 2.8% of all US children aged 5 to 18 [33]. It is both well tolerated and efficacious in the treatment of attention deficit hyperactivity disorder, and is associated with few serious adverse effects [34]. Although there are rare reports of drug interactions between methylphenidate and certain other drugs, they are so infrequent that there is no consistent pattern that can be identified. Toxic concerns with methylphenidate would principally revolve around the abuse of this drug to obtain a stimulant high, and the consequent possibility of developing dependence. A further concern with the long-term use of methylphenidate is the possibility that patients may be at increased risk for psychostimulant abuse. Although when taken orally methylphenidate has a low euphorogenic potential [35], when used intravenously it has an abuse pattern and symptoms of toxicity similar to cocaine and amphetamine [36]. Recent studies in rats also have shown that animals treated with methylphenidate develop behavioral sensitization, suggesting that human users may have increased susceptibility to psychostimulant abuse [37].

Methylphenidate has chiral centers, and exists as enantiomers, although the racemate is used clinically. Studies have shown that the (+)-isomer is responsible for the effect of the racemate [38,39].

![Methylphenidate](image)

**Pemoline.** Pemoline (9), an agent used in treatment of ADHD, has been associated with hepatotoxicity, with the majority of cases occurring in pediatric patients. From its marketing in 1975 up to 1989, 12 cases of acute hepatic failure and 6 deaths associated with pemoline hepatotoxicity had been reported to the FDA [40]. Death generally occurred within 4 weeks of the onset of signs and symptoms of liver failure. In two recent cases, pemoline-induced liver failure required liver transplantation [41].

![Pemoline](image)

Although the absolute number of reported cases is not large, the rate of reporting is 4–17 times higher than that expected in the general population. This estimate may be conservative because of underreporting and because the long latency between initiation of pemoline treatment and the occurrence of hepatic failure may limit recognition of the association. If only a portion of actual cases was recognized...
and reported, the risk could be substantially higher. By contrast, a meta-analysis of the literature by Shevell and Schreiber [42] suggests that the risk of acute hepatic failure may be an overestimate. Nevertheless, because of its association with life-threatening hepatic failure, pemoline should not be considered as a first-line therapy for ADHD. In fact, pemoline has been withdrawn from the Canadian market as a result of this toxicity [43].

Cocaine. The coca plant is a small shrub or tree that is indigenous to South America, where for centuries the leaves have been chewed by the local native populations. The dried leaves of Erythroxylum coca Lamarck, or E. truxillense Rusby, commercially known as Huanuco coca, or Truxillo coca [4], respectively, serve as the raw material for the production of (−)-cocaine (3). Cocaine was first isolated in 1860, and became medically important as an excellent local anesthetic agent, but which is a potent and highly addictive CNS stimulant. The acute toxicity of cocaine derives primarily from its intense sympathomimetic actions. In 1991, an attempt was made to assess the intrinsic toxicity of cocaine by computing the incidence of adverse health outcomes per population of drug abusers. The rates of emergency room visits and deaths were estimated at 15.1 and 0.5, respectively, per 1000 persons using drugs [44].

Acuteely, cocaine can cause anxiety or panic reactions. Used chronically, cocaine can induce a psychosis that closely resembles that produced by amphetamine. It is generally considered that amphetamine psychosis predominantly mimics the positive symptoms of schizophrenia, but in fact stimulant-induced psychosis can mimic a broad range of symptoms, including negative and bizarre symptoms [45]. Paranoid behavior has been produced in experienced cocaine users by continuous (4 h) cocaine infusion [46].

Cocaine can have marked effects on the heart and cardiovascular system. Adverse actions may include myocardial ischemia, cardiac arrhythmias, cardiotoxicity, hypertensive effects, cerebrovascular events, and a hypercoagulable state [25,44]. By 1997, more than 250 cases of myocardial infarction related to the recreational use of cocaine had been documented in the literature [47]. Although less common, aortic dissection related to the use of cocaine-free base ("crack cocaine") has been reported [48]. Seizures also can be associated with cocaine use [49].

In addition to these physiological toxicities, cocaine addicts suffer from a variety of social and economic problems that result in tremendous costs to society. Many of the estimated 1.5 million cocaine addicts in the United States (see www.nida.nih.gov), are underemployed, if they are employed at all, are likely to be involved in drug distribution activities, and typically perform only marginal roles in the legal economic system [50,51]. Adults in such drug-using households rarely engage in conventional behaviors, and often parent children using conduct norms that are structured to produce individuals who have reduced chances to become conventional adults [52].

Caffeine. The psychostimulant action of caffeine generally is accepted as well established. Caffeine quickens reaction time and enhances vigilance, increases self-rated alertness, and improves mood. There is, however, little unequivocal evidence to show that regular caffeine use is likely to benefit substantially either mood or performance. Indeed, one of the significant factors motivating caffeine consumption appears to be "withdrawal relief." [53] The most common symptom of caffeine withdrawal is headache, which typically begins 12–24 h after the last dose of caffeine [54]. Other symptoms of caffeine withdrawal include fatigue, drowsiness, dysphoria, difficulty in concentrating, decreased cognitive performance, depression, irritability, nausea or vomiting, and muscle aches or stiffness [54].

Caffeine can produce adverse and unpleasant effects if doses are increased. Caffeine also has weak reinforcing properties, but with little or no evidence for upward dose adjustment, possibly because of the adverse effects of higher doses. Withdrawal symptoms, although relatively limited with respect to severity, do occur, and may
contribute to continued caffeine consumption [55]. Health hazards are small, if any, and caffeine use is not associated with any type of incapacitation [56]. Acute intake of caffeine does increase blood pressure, with the strongest pressor response in hypertensive subjects. Thus, regular caffeine consumption may be harmful to some hypertension-prone subjects [57]. Some studies with repeated administration of caffeine have shown a persistent pressor effect, whereas in others chronic caffeine ingestion did not increase blood pressure [57]. Epidemiologic studies have produced contradictory findings regarding the association between blood pressure and coffee consumption. During regular use, tolerance to the cardiovascular responses develops in some people, and therefore no systematic elevation of blood pressure can be shown either in long-term or in population studies. The hemodynamic effects of chronic coffee and caffeine consumption have not been sufficiently studied. Finally, caffeine may provoke a panic attack in individuals who suffer from panic or anxiety disorders [58–61].

The psychostimulant properties of caffeine are now generally attributed to antagonism of adenosine A1 and A2 receptors, although the contribution of the respective receptors is still under debate. Recent studies suggest that heterodimers of A1 and A2 receptors may provide a concentration-dependent “switch” by which low and high concentrations of synaptic adenosine produce opposite effects on glutamate release [62]. Recently, an adenosine A2A receptor knockout mouse has been developed that has behavioral symptoms that correspond to functional antagonism of this receptor, similar to the effects of caffeine [63].

3.3. Absorption, Distribution, Metabolism, and Elimination

All substituted amphetamines are strong organic bases, with pKₐ values ranging from 9.5 to 10 [64]. The pKₐ of both cocaine and phenmetrazine is somewhat lower, at 8.5, and methylphenidate has a pKₐ of 8.8 [64]. Thus, these bases are all significantly protonated at physiological pH, and binding to their biological targets probably occurs with the protonated species (for example, see Ref. [65]). These drugs are all administered as their water-soluble salts, usually hydrochlorides or sulfates. Of course, at physiological pH these bases exist in an equilibrium between the protonated ionized form, and the unprotonated unionized species. The latter free bases are lipid soluble and readily penetrate the brain, where they exert their CNS stimulant effects. Many of these drugs are eliminated in the urine unchanged because acidic urine leads to a higher fraction of protonated species, thus decreasing reabsorption of the unchanged drug in the renal tubules. Decreasing urinary pH by, for example, administering ammonium chloride leads to the anticipated increased urinary excretion and reduced duration of action [66]. A comparison has been reported of the urinary excretion pattern of methamphetamine in humans, guinea pig, and rat [67]. In humans, 23% of the dose was excreted unchanged. Ring-hydroxylated and N-demethylated metabolites were excreted as 18% and 14% of the dose, respectively.

Amphetamine metabolism. The metabolism of (+)-amphetamine 10 is variable, depending on the species studied. Possible metabolic transformations involve hydroxylation at the alpha- or beta-side-chain carbon atoms, on the nitrogen atom, and at the para position of the aromatic ring. These metabolites can then be further oxidized, or conjugated and excreted. One or more of these pathways predominates, depending on which animal species is being studied. In man, the half-life of (+)-amphetamine has been reported as 7 h [68]. Approximately 30% of the dose of racemic amphetamine is excreted unchanged, and acidification of the urine can decrease the half-life significantly [69,70]. In man, the principal metabolite is benzoic acid [71]. The details of the sequences of metabolic reactions of amphetamine that lead to benzoic acid have not been elucidated [68], but the beta-hydroxylated metabolite, norephedrine, also has been identified as a metabolite in man [72].
The metabolism of methamphetamine 11 involves both N-demethylation and ring hydroxylation. Caldwell et al. [67] reported that in humans 22% of the administered dose was excreted as unchanged drug, and 15% as the 4-hydroxylated compound.

Methylphenidate metabolism. The metabolism and pharmacokinetics of methylphenidate have been studied extensively. Methylphenidate 8 is administered as the racemic threo isomer, but the (−)-threo enantiomer is more rapidly metabolized. Methylphenidate is an ester, and the methyl ester is rapidly cleaved. The ester hydrolysis product, called ritalinic acid, comprises approximately 80% of the urinary metabolites after an orally administered dose [73]. Ritalinic acid is not pharmacologically active. The lability of the ester function is probably the major factor limiting the oral bioavailability of methylphenidate to between 10% and 50% [74]. A ring-hydroxylated ritalinic acid metabolite (2%) also has been identified. Other minor pathways involving oxidation of the piperidine ring (oxo-ritalin) and conjugation reactions represent less than approximately 1% of the administered dose [32].

Cocaine metabolism. Cocaine 3 has two ester functions, and both can be hydrolyzed in vivo to generate metabolites. Hydrolysis of the methyl ester leads to benzoylecgonine 12,
and hydrolysis of the benzoyl ester leads to ecgonine methyl ester 13. Tropan-3β-ol-2β-carboxylic acid is known as ecgonine 14. In cocaine users who also consume significant amounts of ethanol, a transesterification product (cocaethylene 15) is also detected. Cocaethylene is also a potent psychostimulant, with approximately four times higher potency as a local anesthetic than cocaine itself [75], and can enhance the cardiotoxicity associated with cocaine use.

Diethylpropion metabolism. Diethylpropion 16, is used most extensively as an appetite suppressant. It possesses the core phenethylamine structure characteristic of many psychostimulants, but is a tertiary amine ketone. It is extensively metabolized in man, with only approximately 3–4% of the drug excreted unchanged. Alpha-alkylamino ketones are apparently N-dealkylated readily and thus, the principal metabolite is the N-deethylated compound 17, comprising approximately 35% of the administered dose. Reduction of the carbonyl is less important, with approximately 20% of the dose going that route to afford N,N-diethylnorephedrine. Approximately 30% of the dose cannot be accounted for as an amine product in the urine and is probably a deaminated metabolite [76]. Studies by Yu et al. [77] found that the N-deethylated metabolite 17 was probably responsible for the pharmacological effects of diethylpropion 16. These workers reported that the N-monethyl metabolite 17 was a substrate at the norepinephrine and serotonin transporters and an inhibitor at the dopamine uptake transporter, whereas (1R,2S) and (1S,2R)-N,N-diethylnorephedrine as well as diethylpropion itself were inactive in those assays.
4. PHYSIOLOGY AND PHARMACOLOGY

4.1. Where and How These Drugs Work

Neurons in the central nervous system communicate by chemical transmission. Of relevance to the present discussion are monoamine neurons that release dopamine, norepinephrine, or serotonin as one of their transmitters in response to an action potential. Reuptake transporter proteins embedded in the neuronal plasma membrane then clear the synapse of monoamines, typically taking up 70–80% of the released transmitter. This reuptake is thought to be the major termination mechanism for the monoamine chemical signaling process.

All psychostimulants appear to elevate synaptic levels of dopamine and norepinephrine. In addition, cocaine, and to a lesser extent some of the other agents also raise synaptic levels of serotonin. It is the current consensus that elevated dopamine levels lead to CNS stimulation and are responsible for the reinforcing properties of stimulants [78–84]. It is now widely accepted that mesocortical dopamine plays a critical role in drug reward [85].

There are two principal mechanisms for increasing synaptic monoamine levels. One is to block the reuptake of neurotransmitter after its excitation-coupled release from the neuronal terminal. Thus, blocking the action of the uptake carrier protein prevents clearance of the neurotransmitter from the synapse, leaving high concentrations in the synaptic cleft that can continue to exert a signaling effect. This mechanism is the one invoked to explain the action of cocaine, a potent inhibitor of monoamine reuptake at the dopamine, serotonin, and norepinephrine transporters, and of methylphenidate, which is a reuptake inhibitor at the dopamine and norepinephrine transporters [86]. It should be noted, however, that methylphenidate also has the ability to induce the release of catecholamines stored in neuronal vesicles [87,88].

The second mechanism is the one more relevant to the action of amphetamine and related agents. This mechanism is illustrated in Fig. 1. Biogenic amine transporters, which include the dopamine transporter (DAT), norepinephrine transporter (NET), and serotonin transporter (SERT) are the targets for psychostimulant drugs. These proteins are members of the neurotransmitter/sodium symporter (NSS) family [89]. Amphetamine, and other small molecular weight compounds with similar structures, are substrates at the monoamine uptake carriers and are transported into the neuron (Fig. 2). The uptake carrier has an extracellular and intracellular face, and after transporting a substrate (amphetamine, etc.) into the neuron, the intracellular carrier face can bind to dopamine and transport it back to the extracellular face.

Figure 1. Amphetamine interacts with the dopamine transporter protein, 1, and is transported inside. After being transported inside the terminal, high concentrations of amphetamine can displace dopamine from vesicular storage sites 2, leading to elevated cytoplasmic levels of dopamine 3. After amphetamine dissociates on the intraneuronal surface, dopamine binds to the carrier 4. The carrier then transports dopamine to the extracellular face 5, driven by the favorable concentration gradient, where the dopamine dissociates and leaves the carrier available for another cycle. This overall process is referred to as the alternating access model of molecular transport [90,91].
This exchange diffusion mechanism is calcium independent, and is capable of robustly increasing synaptic transmitter levels. This process is often described as a “reversal” of the normal uptake carrier process.

The substrate binding site is located near the center of the protein in the membrane, and has “alternating access” to either side of the membrane, resulting from reciprocal opening and closing of the cavities that connect the binding site to either side of the membrane. The energy for transport is primarily derived from the Na\(^+\) gradient. Intracellular levels of Na\(^+\) are kept low by active pumping out of the cell. The resulting inward Na\(^+\) gradient, coupled with the negative membrane potential, is the source of the energy used to drive substrates into the cell. A more detailed look into the mechanics of this process has been developed from recent studies of crystal structures for the NCS1 benzyl-hydantoin transporter from *Microbacterium liquefaciens* [92].

Whereas the CNS stimulant effects of these molecules depend on an action in the brain, uptake inhibitors and substrates at peripheral monoamine carrier sites obviously can exert other physiological effects. Cocaine is an excellent local anesthetic agent. Furthermore, its potent inhibition of norepinephrine reuptake leads to stimulation of alpha-adrenergic receptors, causing local vasoconstriction that delays the diffusion of the anesthetic agent out of the tissue. Similarly, users who chronically insufflate cocaine into their nasal passages often develop necrotic lesions due to the local vasoconstricting effect of cocaine, again due to the blockade of norepinephrine reuptake. Not surprisingly, cocaine and amphetamines have effects on the cardiovascular system, by virtue of their ability to enhance indirect adrenergic transmission at peripheral sites. Knowledge of the physiology of the sympathetic nervous system and the functions of peripheral adrenergic nerve terminals allows a relatively straightforward prediction of the types of drug effects produced by monoamine uptake inhibitors or releasing agents.

Nevertheless, recent studies have begun to focus attention on glutamate systems as potential key components of the actions of psychostimulants. For example, Swanson et al. [93] have shown that repeated cocaine administration leads to long-term attenuation of group I metabotropic glutamate receptor function in the nucleus accumbens. In particular, this functional reduction was related to significantly reduced mGluR5 immunoreactivity in the medial nucleus accumbens. Even more exciting is the report that mGluR5 knockout mice do not display the reinforcing and locomotor effects of cocaine, in spite of the fact that cocaine administration increases extracellular dopamine in the nucleus accumbens of these mice to levels that do not differ from wild type animals [94].

Group III mGlR agonists have also been shown to have profound effects when administered with psychostimulants. For example,
a nonselective group III mGluR agonist attenuated the amphetamine- or cocaine-induced increases in locomotion and striatal dopamine [95–97]. Among the group III mGluRs, the metabotropic glutamate receptor 7 (mGluR7) has the highest expression in brain regions involved in reward phenomena [98–100]. AMN082, a selective mGluR7 agonist, dose-dependently inhibited the rewarding effects of cocaine, as assessed by electrical brain stimulation reward and cocaine self-administration in rats [101]. The effect was blocked by coadministration of a selective mGluR7 antagonist. In the near future, the role of glutamate systems in the actions of psychostimulants likely will be more fully elucidated, resulting in new approaches to the treatment of conditions that now respond to classical stimulants.

4.2. Biochemical Pharmacology: Receptor Types and Actions

The monoamine reuptake carrier proteins (targets of the psychostimulants) are members of a larger Na⁺/Cl⁻ symporter family that includes a number of other proteins, including the GABA transporters, amino acid transporters, and orphan transporters [102]. The primary amino acid sequence of the monoamine transporters is highly conserved, with several regions of these proteins having high homology [103]. It is presently believed that all of the members of this family possess a membrane-spanning 12 alpha-helix motif, with a single large loop containing glycosylation sites on the external face of the membrane (Fig. 3). Members of this family of proteins have been identified not only in mammalian species but also in eubacteria and archeobacteria, indicating their very early emergence in the evolution of life.

The human norepinephrine uptake transporter was first sequenced and then expressed in HeLa cells in 1991 [104] and found to have properties identical to those of the native transporter. The cloning and sequencing of the dopamine transporter [105–107] and the serotonin transporter [108,109] were reported in the same year. There are a number of excellent review articles written about monoamine transporters [102,103,110–112]. The most exciting recent development is the construction of homology models of the dopamine [113,114] and serotonin [115,116] transporters, derived from the 1.65 Å X-ray crystal structure of the bacterial Leucine transporter (LeuT), from *Aquifex aeolicus* [117].

Pharmacological studies of the mechanism of action for psychostimulants in animals have

![Figure 3. Representation of the 12 helix transmembrane transporter protein family from the X-ray crystal structure of the *Aquifex aeolicus* leucine transporter [117]. (a) Side view, looking in the plane of the cell membrane, with the extracellular side toward the top. (b) The top view, looking from the extracellular face of the transporter. Both the amino terminus and carboxyl terminus are intracellular, with the second extracellular loop being larger, and possessing glycosylation sites. For clarity, all of the loops are not displayed. The extracellular side is toward the top of the figure, and the intracellular surface toward the bottom. Leucine and two sodium ions are visible in the center of the bundle, represented as space-filling models.](image-url)
The conclusions of those studies have generally been extrapolated to humans, with little clinical evidence until recently to support these ideas. In the past several years, however, clinical studies of several stimulants, using in vivo brain imaging either with SPECT techniques or with PET techniques, has provided evidence for elevated extracellular dopamine in response to psychostimulant administration. In essence, these studies employ either a single photon- or a positron-emitting dopamine receptor antagonist. The labeled antagonist is administered both in the absence and in the presence of the stimulant drug of interest. The imaging technique then is used to determine how much of the labeled ligand has been displaced from its receptors by competition from increased extracellular endogenous dopamine. Based on the known affinity of the labeled ligand for its dopamine receptor, calculations can determine the increased concentration of dopamine that must have been available at the receptors. These definitive studies have clearly established a role for dopamine in the effects of stimulants in humans [78,80].

This type of approach has recently been applied to the study of methylphenidate. For example, Booij et al. [120] used SPECT imaging and an $[^{123}]$I-benztamide dopamine D$_2$ receptor ligand antagonist ($[^{123}]$IBZM) to measure significant displacement of the ligand by endogenous dopamine that had been released in response to administration of methylphenidate. In related work, Volkow et al. [80] used $[^{11}]$C-$(+)$-threo-methylphenidate to show that greater than 80% occupancy of the dopamine transporter was required to produce the stimulant “high.” With the dopamine D$_2$ receptor antagonist $[^{11}]$C-raclopride, Volkow et al. [121,122] showed that the intensity of the methylphenidate “high” was quantitatively correlated with the levels of released dopamine and dopamine D$_2$ receptor occupancy. Subjects who perceived the most intense high had the highest increases in extracellular dopamine. Conversely, no high was experienced by subjects when methylphenidate did not increase dopamine levels. In a second study, using the same methodology, this same group [123] found that subjects who “liked” the effects of methylphenidate had significantly lower dopamine D$_2$ receptor levels than subjects who disliked its effects. The authors speculated that lower D$_2$ receptor density might be a factor contributing to psychostimulant abuse by providing a more pleasurable response. These imaging studies illustrate how data from animal research can now be validated in humans.

Because the stimulants cause increased synaptic levels of dopamine, and other monoamine neurotransmitters, they indirectly lead to stimulation of various postsynaptic receptors through the increased concentrations of neurotransmitter. A large number of animal studies have been reported using various agonists and antagonists to elucidate the role of different dopamine receptor isoforms. Until recently, however, only nonspecific ligands (i.e., with effects on both the D$_1$-like and D$_2$-like families) were available. In drug discrimination studies, rats have been trained to recognize and discriminate the interoceptive cues produced by injection of amphetamine or cocaine [124]. Administration of the partial but selective D$_1$-receptor agonist SKF 38393 was partially recognized by the cocaine-trained rats, but not by amphetamine-trained animals. Yet, both amphetamine- and cocaine-trained rats discriminated the cue produced by the dopamine D$_2$ agonist bromocriptine as being similar to their training drugs. A dopamine D$_3$-selective agonist produced cocaine responses, but was only partially recognized by amphetamine-trained rats. Following additional experiments with dopamine receptor subtype selective antagonists, the authors concluded that the dopamine D$_2$ receptor played an essential role, but that both the D$_1$ and D$_3$ receptors might have some less important function. There is an extensive present research effort underway in many laboratories that is attempting to elucidate both the anatomical substrates and the specific postsynaptic receptor isoforms that are important in the various actions of psychostimulants.

A role for serotonin? Although the conventional wisdom is that stimulants elevate synaptic dopamine, it is not at all clear that this
sole mechanism is responsible for the spectrum of effects produced by the psychostimulants. In addition, it is becoming evident that animal models used to understand the stimulants must consider mechanisms underlying effects on locomotor activity somewhat differently from those that govern either reward or drug discrimination phenomena [125,126]. The use of mice genetically deficient for the serotonin or dopamine transporter (“knockout mice”) has produced some particularly interesting findings. For example, knockout mice lacking the DA transporter have high levels of extracellular dopamine, a condition that would presumably mimic the pharmacological action of cocaine. Consistent with this prediction, they display spontaneous hyperlocomotion [127]. Surprisingly, however, these mice still self-administered cocaine [128]. Further experiments in these mice indicated the probable involvement of the serotonin transporter. In addition, conditioned place preference, another animal model of the reinforcing quality of a drug, could be established for cocaine in mice lacking either the dopamine transporter or the serotonin transporter [129]. Similarly, place preference also could be established for methylphenidate, another stimulant that is thought to work through dopamine mechanisms, in mice lacking the dopamine transporter.

Experiments with knockout mice often produce unexpected results. It must be kept in mind, however, that when a key protein is missing during neural development, the offspring may have some type of adaptation that does not occur in the wild type organism. Some caution, therefore, must be exercised in interpreting the results. For example, Belzung et al. [130] found that mice lacking the serotonin 5-HT₁B receptor failed to display conditioned place preference. When, however, these knockout mice were compared in studies using classical pharmacological antagonists of the 5-HT₁B receptor, divergent results were obtained. The 5-HT₁B Receptor knockout mice had an increased locomotor response and increased propensity to self-administer cocaine [131]. By contrast, a 5-HT₁B receptor antagonist attenuated cocaine-induced locomotor effects but had no effect on cocaine self-administration [132]. The authors point out that compensatory changes during development of the knockout mice may have rendered them more vulnerable to the effects of cocaine.

Nonetheless, there is a vast body of literature documenting interactions between dopamine and serotonin pathways in the brain [133–137]. Clearly, however, if a drug (e.g., cocaine) releases multiple transmitters, then a behavioral interaction is not surprising. Inhibition of presynaptic reuptake of serotonin, for example, no doubt leads to postsynaptic activation of a variety of other receptors, some of which could modulate dopamine function. In addition to potential effects on 5-HT₁B receptors, other studies have implicated serotonin 5-HT₄ receptors [138], 5-HT₂A receptors [139], and 5-HT₂C receptors [140]. 5-HT₁A receptors also can modulate the locomotor effects of cocaine [141].

A role for norepinephrine? Although the vast majority of studies of psychostimulants have focused on the role of dopamine and/or serotonin, the importance of norepinephrine (thought to be paramount 35 years ago) generally has been overlooked. Details of the mechanism of action of psychostimulants have been developed primarily using animal models, in which dopamine seems to be the key player, and these results then have been extrapolated to man. Yet cocaine also is a potent NE uptake inhibitor, and the potency of amphetamine for norepinephrine release is similar to that for dopamine release. Indeed, in the rat prefrontal cortex, amphetamine and cocaine increased extracellular norepinephrine to an extent that was quantitatively similar to that of dopamine [142]. Further, it appeared that the increase in prefrontal cortical norepinephrine was actually due to the blockade of the norepinephrine transporter by both drugs. Recently, Rothman et al. [143] reported that the oral doses of several stimulants required to produce amphetamine-like subjective effects in humans were most closely correlated with their ability to release NE, and not DA. Further, their ranking in subjective effects did not correlate with decreased plasma prolactin, a response that is mediated by dopamine receptor stimulation. These authors suggested that NE might contribute to the amphetamine-like
psychopharmacology of stimulants, at least in humans.

Until clinical studies are carried out using receptor blockers and specific norepinephrine transporter inhibitors, this area will remain muddy, at best. In virtually every example, from amphetamine to cocaine, the compounds have significant effects at the norepinephrine transporter, in some cases equal to or even greater, than at the dopamine transporter. When behavioral or mood changes are correlated with levels of extracellular dopamine, and dopamine is highly correlated with changes in extracellular norepinephrine, one cannot be certain which underlying pharmacology is ultimately more important without experiments using specific blockers of both dopamine and norepinephrine transporters and receptors. It may be that effects on dopamine are necessary, but not sufficient, and that both norepinephrine and serotonin play modulatory roles. Because the stimulants have such diverse effects, including increasing activity, mood, appetite suppression, etc., it seems likely that serotonin and norepinephrine play more or less important modulatory roles, depending on which aspect of the specific drug’s effects are being studied.

In a related vein, the subjective psychostimulant effects of amphetamine were attenuated following a 2 h pretreatment with a tyrosine- and phenylalanine-free amino acid mixture [144]. These amino acids are biosynthetic precursors of the catecholamines, and deprivation would be expected to produce transient reductions in endogenous dopamine and norepinephrine. The authors concluded that tyrosine depletion attenuates the release of dopamine required for the psychostimulant effect. Interestingly, the pretreatment did not reduce the subjective appetite suppressor (anorectic) effect of amphetamine. The study authors attributed this latter finding to a continued release of norepinephrine by amphetamine. Tyrosine depletion, however, would also attenuate norepinephrine biosynthesis and it may be more reasonable to conclude that the anorectic effect might be related to the often-overlooked ability of amphetamine to release neuronal serotonin.

This chapter will make no attempt to review all the literature that focuses on the role of norepinephrine and serotonin in the actions of psychostimulants. At the time of this writing, the general consensus seems to be that effects on dopamine systems are necessary, but perhaps not sufficient conditions to explain all the different actions of stimulants. There appears to be increasing awareness, spurred initially by studies of cocaine, that serotonin may be a much more important player than was heretofore recognized. In the next few years, this role likely will be studied and elucidated in much greater detail.

**Psychostimulant sensitization.** Repeated administration of amphetamine over a short period of time to rats, monkeys, or humans leads to a persistent behavioral sensitization to a subsequent low dose amphetamine challenge [145–148]. Long-lasting changes in brain neurochemistry and morphology also are observed following amphetamine sensitization [149]. In rodents, repeated exposure to amphetamine or cocaine leads to persistent changes in dendrite structure and dendritic spines in brain areas involved in incentive behavior, motivation, and judgment and inhibitory control of behavior [150]. This reorganization of synaptic connectivity is speculated to contribute to persistent behaviors associated with psychostimulant abuse, including addiction.

**Caffeine** and the other methylxanthines inhibit phosphodiesterases, the enzymes that degrade cAMP. For many years, it was believed that the stimulant effect of caffeine was due to this enzyme inhibition. At the plasma concentrations obtained after two to three cups of coffee (ca. 10 μM), however, antagonism of adenosine A2A (and A1) receptors in brain is believed to be the most relevant action to explain the stimulant effects of caffeine [151,152]. Perhaps not surprisingly, in view of earlier discussion in this chapter, caffeine administration has been shown to lead to elevated levels of brain dopamine [153,154]. It is thought that adenosine receptor stimulation facilitates GABA- or acetylcholine-mediated inhibition of dopamine receptors in striatopallidal and striatonigral neurons [155], with the end result of decreased dopaminergic function; adenosine antagonists would thus have a reverse action. Many studies have examined the interaction...
between adenosine A2A receptors and dopamine receptors, both of which are highly concentrated and colocalized in the striatum and have reciprocal antagonistic interactions [156–159]. There is abundant evidence for pre- and postsynaptic interactions between adenosine and dopamine receptors, by which adenosine inhibits dopaminergic activity (for example, see Ref. [160]).

With respect to stimulation of locomotor activity in animal models, studies have implicated the dopamine D2 receptor [161,162]. It has not been clear, however, whether effects mediated by striatal adenosine A2A receptors absolutely depend on the presence of dopamine D2 receptors. To study this problem, Chen et al. [163] employed either genetic knockout mice deficient in dopamine D2 receptors, adenosine A2A receptors, or a double knockout mouse deficient in both types of receptors. These studies found that A2A receptors may affect neuronal activity in a manner that is partially independent of the presence of dopamine D2 receptors, such that endogenous adenosine may be most accurately viewed as a facilitative modulator of striatal neuronal activity rather than simply as an inhibitory modulator of D2 receptor neurotransmission.

These studies, and many others, conclude that the acute locomotor stimulant effects of caffeine in animal models are mediated in part by dopaminergic systems and dopamine receptors. Recent studies suggest that tolerance to the locomotor stimulant effects of chronic caffeine also may be related to specific changes in dopaminergic function [160]. Thus, in spite of the fact that methylxanthines are structurally different from other psychostimulants, and do not directly affect dopamine transporters or receptors, in fact their stimulant action appears to be derived from effects on central dopaminergic pathways.

5. STRUCTURE–ACTIVITY RELATIONSHIPS

Examination of the structure–activity relationships of several of the classic stimulants provides not only an understanding of the development of other drugs but also important clues as to the underlying mechanisms involved in interaction with the target protein(s). The following sections will hopefully illustrate both of these points.

5.1. Amphetamine

There are a number of related structures that are often referred to as “amphetamine” although the name amphetamine refers to one specific molecular entity. Grouped in this class would be (+)-amphetamine 10, N-methamphetamine (S-(+)-methamphetamine 18), phentermine 19, phenmetrazine (Preludin, 20), and phendimetrazine 21. Diethylpropion (Tenuate®; 16) is used as an appetite suppressant and, although it has the amphetamine skeleton, its effects are much weaker as a stimulant than the other structures listed here. The stereochemistry at the alpha-side-chain methyl group is the same for the most potent enantiomer of each structure, although the pure enantiomer has not generally been marketed except for the cases of (+)-amphetamine 10 and (+)-methamphetamine 18.

The structural requirements of the dopamine (and norepinephrine) transporter for substrates appear to be fairly rigid. There is very little molecular variation that is tolerated without significant loss of activity. The relatively limited information that is available, mostly from animal studies, can be summarized by considering the various areas of substitution for a general phenethylamine structure. These structure–activity relationships recently have been surveyed [164],
and an extensive and comprehensive review by Biel and Bopp [165] covered the older literature.

5.1.1. Length of the Side Chain  The length of the side chain is limited to two carbon atoms [166,167]. That is, for transporter substrates, the optimum pharmacophoric template appears to be a basic nitrogen two carbon atoms removed from an aromatic ring system. This observation of course is not too surprising because the transporter substrates dopamine, norepinephrine, and serotonin all bear this essential core.

5.1.2. Nitrogen Substituents  Tolerated nitrogen substituents are very limited. The primary amine (amphetamine) and the N-methylamine (methamphetamine) are the most potent compounds [167]. An N-methyl increases the potency of both amphetamine and cathinone 2 [168]. Larger alkyl groups [167,169] or N,N-dialkylation, either dramatically attenuate or completely abolish stimulant activity [170]. Nevertheless, N,N-dimethylamphetamine has appeared on the illicit market [171], and does appear to have behavioral effects in rats and monkeys similar to amphetamine [170,172]. The rapid onset of action suggested that the N,N-dimethyl compound itself had pharmacological effects, rather than the N-demethylated metabolite, methamphetamine, although the latter is one of the known metabolites of N,N-dimethylamphetamine [173].

Active metabolites may be much more important in N,N-dialkylated compounds that possess a beta-keto function, as in cathinone 2. In that case, the N,N-dimethyl compound is nearly as active as the N-monomethyl compound [174]. It is known, however, that the alkyl groups of beta-aminoketones are readily cleaved metabolically. Thus, the N,N-dimethyl cathinone analog is likely rapidly converted in vivo to the N-monomethyl compound methcathinone. This argument is consistent with the finding that the N-monoethyl metabolite is the active species following administration of diethylpropion, the N,N-diethyl congener of cathinone [76,77].

Although longer N-alkyl groups lead to less active compounds, one exception to this generalization is benzphetamine (Didrex), N-benzyl-N-methylamphetamine 22. Despite the N,N-dialkyl groups in benzphetamine, in humans it produces subjective effects characteristic of amphetamine-like drugs such as phenmetrazine 20 [175]. Although para-hydroxy-N-benzylamphetamine is a major metabolite of benzphetamine, methamphetamine and amphetamine also are detectable in urine and hair following administration of benzphetamine [176–178]. It is not clear from the literature whether the reinforcing effects of benzphetamine are due to metabolic formation of amphetamine or methamphetamine. Based on the studies with N,N-dimethylamphetamine by Witkin [170], however, one would predict that the parent molecule has some pharmacological activity.
5.1.3. Stereochemistry at the Alpha-Carbon
The stereochemistry at the alpha-carbon atom, when enantiomers exist, is homochiral to that of $S$-$(+)$-amphetamine 10, shown earlier. Both the releasing actions at dopamine and norepinephrine transporters in isolated rat brain slices [179], and the locomotor and stereotypic effects in rodents [180] are more potently affected by the $S$-$(+)$ isomer of amphetamine than by the $R$-$(−)$ isomer. In this latter study, the $(+)\text{ enantiomer was approximately five times more potent than the } (−)\text{ isomer, paralleling the potency difference found with the enantiomers in vitro, using rat brain striatal synaptosomes [181]. The two isomers were of nearly equal potency in their effects on norepinephrine accumulation by rat hippocampal synaptosomes [181]. This stereochemical requirement applies to beta-keto derivatives as well; the corresponding active isomer has the $S$-$(−)$ configuration [168].}

5.1.4. The Alpha-Alkyl Substituent
The alpha-alkyl group cannot be much larger than a methyl. Phenethylamine itself, lacking the side-chain alpha-methyl group, is inactive in vivo, as a result of rapid inactivation by monoamine oxidase. Addition of the alpha-methyl group retards metabolism by this route, leading to the orally bioavailable drug amphetamine. The uptake transporter, however, cannot tolerate large groups in this region and the alpha-ethyl analogs of both amphetamine and methamphetamine had markedly attenuated activity in a drug discrimination assay with rats trained to discriminate $(+)$-amphetamine [182]. Alpha-alpha-dimethyl groups, as in phentermine 19, result in an active compound, but one with reduced activity.

Attempts to incorporate the side chain into ring structures also lead to compounds with attenuated activity. For example, in drug discrimination assays using rats trained to recognize the effect of $(+)$-amphetamine 10, compounds 23 and 24 either failed to produce amphetamine-like effects or had much lower potency [182,183]. When $n = 3$, the compound lacked any amphetamine-like action.

5.1.5. Other Side-Chain Substitutions
Limited substitution of the side chain is tolerated. A beta-hydroxy group on methamphetamine gives ephedrine 1, shown earlier. Although ephedrine is a CNS stimulant, its effects are much weaker than those of methamphetamine. Similarly, addition of a beta-hydroxy to amphetamine gives phenylpropanolamine, a compound that is nearly devoid of CNS stimulant effects. One may speculate that the polar hydroxy group reduces the hydrophobicity of these compounds such that CNS penetration is dramatically reduced. The $N$-methyl of ephedrine increases lipid solubility, so ephedrine has greater CNS action than phenylpropanolamine. Addition of a keto function to the structure of amphetamine or methamphetamine gives cathinone 2 or its corresponding $N$-methyl derivative, methcathinone, the latter which also has greater potency than the primary amine [174]. It should be noted that an oxygen at the beta-position can be incorporated into a heterocyclic ring as in phenmetrazine 20 and phendimetrazine 21. Methyl aminorex, 25, is also a potent stimulant that incorporates the essential features of the amphetamine template into an oxazoline ring. The $4S,5S$-trans isomer shown (25) is the more potent of the four possible stereoisomers [184,185].

5.1.6. Aromatic Ring Substitution
Simple ring substituents can change the targets of the amphetamines from one monoamine uptake carrier to another. The dopamine and norepinephrine uptake carrier proteins have
the most stringent structural demands, and any ring substitution decreases their potency at these sites. The serotonin carrier is relatively promiscuous, and tolerates a variety of ring substituents, many of which dramatically increase the potency at the serotonin carrier relative to that of amphetamine itself. No ring modifications are known that give rise to a substituted amphetamine that completely retains amphetamine-like psychostimulant activity. Para-fluoroamphetamine (26; X = F) has been reported to have effects in rats resembling those of amphetamine, but substitution with larger halogens (e.g., chloro or iodo) leads to compounds that have significant serotonin releasing potency, and which produce behavioral effects different from those of amphetamine itself [186].

\[ \text{CH}_3 \text{NH}_2 \]

\[ \text{X} \]

\[ \text{OCH}_3 \]

\[ \text{Cl} \]

5.2. Methylphenidate

The \( R,R- (+)-\)-stereoisomer of methylphenidate 8 is known to be the more active [187], and is often referred to as the active “threo” isomer. The \( (-)-\)enantiomer and the erythro stereoisomers are much less potent. One study has reported a series of aromatic ring-substituted analogs. The most potent compounds in that report were halogen substituted in the 3-, or 3,4- positions of the ring. For example, the dichloro compound 27 was 32-fold more potent than methylphenidate itself in inhibiting dopamine reuptake [188]. That finding parallels a recent report by Deutsch et al. [189], that replacing the phenyl ring with a beta-naphthyl moiety [190] gave a compound with approximately eightfold higher affinity for the dopamine transporter. Those workers also reported that the corresponding alphaphnathyl analog had only approximately one-tenth the potency of methylphenidate at the DAT. Taken together, these latter observations indicate that the DAT must have a hydrophobic region that generally extends from the 3,4-positions of the aromatic phenyl ring of methylphenidate.

Deutsch et al. [189] also examined the effect of heterocyclic ring size. The pyrrolidyl and azepino, as well as the azacyclooctane congeners were significantly less potent than methylphenidate itself. That report also contained data for the morpholine analog of methylphenidate [190], which had approximately 15-fold lower affinity at the DAT. Beyond the studies cited here, very little additional SAR work has been done with methylphenidate.

5.3. Cocaine

Of all the psychostimulants, cocaine probably has been most studied, particularly within the last decade, as a result of its widespread abuse. Structure–activity studies have been carried out with numerous analogs, not only to elucidate the molecular requirements for interaction with the various monoamine transporters but also in attempts to develop treatments that might be useful for cocaine addiction. Ideally, understanding the structure–activity relationships will be useful to understanding the functional topography of the binding site of the transporters. Nevertheless, because the topic of this chapter is stimulants, and not the structure–activity relationships of monoamine transporters, an exhaustive summary of the more numerous studies that have appeared on the SAR of cocaine and its analogs will not be presented. A useful perspective on the SAR of cocaine analogs as it was understood in 1992 has been presented by Carroll et al. [191], with more a recent update in 1997 [192].

An attempt will be made here to distill down the essence of the SAR of cocaine as it relates to its stimulant properties. In many cases, compounds have been reported that have not been tested \textit{in vivo}, but have been
compared only for affinity at the monoamine transporters, or in an in vivo assay. Some of these data will be summarized if they are reported in the context of the stimulant effects of cocaine. Similarly, there have been numerous attempts to develop cocaine analogs that may bind to the dopamine transporter and actually block the stimulant or reinforcing effects of cocaine itself, in efforts to develop treatments for cocaine addiction. This chapter largely ignores many of those studies unless they contain in vivo data suggesting they are relevant to a discussion of stimulant effects. Nevertheless, because stimulant properties have been associated with binding to the DAT, a good deal of the SAR discussion here must be discussed in the context of in vitro DAT affinity.

A consideration of the structure–activity relationships of cocaine can focus on a number of key elements in the structure, as indicated below. Each of the following sections will include a discussion of the particular numbered structural element.

5.3.1. N-Substituents  N-demethylation of cocaine has only a minor effect on affinity at monoamine transporters [193]. In phenyltropane analogs where the ester linkage has been removed (e.g., 28), extensions of the N-alkyl out to n-butyl have no effect on dopamine transporter affinity [194]. Effects at the serotonin transporter are variable, but affinity only decreases modestly. At the norepinephrine transporter, affinity drops approximately threefold with the longer N-alkyl group.

5.3.2. Basic Nitrogen Atom  For many years it was assumed that the basic nitrogen of cocaine was required for activity. It seemed logical to believe that the nitrogen, protonated at physiological pH, would interact with an anionic site such as an aspartate residue in the transporter [195]. It was surprising, therefore, when nonbasic N-sulfonyl cocaine analogs such as 29 were found to possess high affinity for the dopamine transporter [196]. These compounds are not protonated at physiological pH, and if hydrogen bonding were required for activity, these analogs could only serve as hydrogen bond acceptors. Even then, the low electron density remaining on a nitrogen with the powerfully electron-withdrawing trifluoromethylsulfonyl group attached, would suggest that this interaction should be very weak.

Replacement of the nitrogen atom with oxygen as in 30 gives compounds that retain high affinity for the dopamine transporter [197]. This finding was accommodated by proposing that the oxygen atom could act as a hydrogen bond acceptor at the transporter [197], a conclusion that would at least be consistent with the activity of the N-sulfonated derivatives 29.

It was even more surprising; therefore, when the report appeared that even a polar oxygen was not required for good uptake inhibitors. Carbocyclic compounds such as 31 proved to have transporter affinities nearly
equal to their amine-containing counterparts [198]!

These authors postulated that there are various acceptor sites in the dopamine transporter, where an inhibitor may bind and cause dopamine uptake inhibition. The topography of these sites is probably different in the three monoamine transporters.

5.3.3. Substituent at C(2) Epimerization of the ester function to give pseudo-cocaine 32 results in approximately a 150-fold loss in affinity for the dopamine transporter [193]. In compounds lacking the ester linkage (see Section 5.3.4) the effect is more dramatic, resulting in a more than 1000-fold lower potency.

The ester is not an essential function. Replacement of the ester with an ethyl or vinyl group did not lead to significant loss of binding affinity, demonstrating that a polar function capable of hydrogen bonding was not essential [199,200]. Indeed, substitution at the 2β-position with alkyl groups as long as n-butyl, 2-phenethyl, or 2-stryl gave compounds (e.g., 33) with exceptionally high affinities at the dopamine transporter [200].

Kelkar et al. [201] have extended the 2β-alkyl group to include a polar hydroxy or methyl ester function at the distal end of a three carbon chain, with no significant loss of affinity compared to a simple carbomethoxy function. They concluded that this region of the cocaine binding site must be either a large cleft in the transporter protein or exterior to the binding site. They also noted that this region is relatively insensitive to electrostatic interactions. Chang et al. [202], found that the 2β-phenyl analog 34 was equipotent to the 2-carbomethoxy compound, but had enhanced selectivity for the dopamine transporter over the serotonin transporter. These authors also concluded that a hydrophobic group at this region of the molecule might be a contributing factor for binding at the dopamine transporter.

Esters larger than a methyl are quite potent. In the 3-benzoyl series of tropane esters, both the isopropyl and phenyl esters had high affinity and selectivity for the dopamine transporter [203]. The phenyl ester (35; RTI-15) dose-dependently substituted in the drug discrimination paradigm in rats trained to discriminate the effects of cocaine. In contrast, whereas cocaine increased locomotor activity in mice, RTI-15 had no effect on activity and at high doses even decreased this measure [204]. This compound was a potent inhibitor of the dopamine transporter, suggesting that high selectivity for the dopamine transporter may lead to differential retention of cocaine-like effects.

The isopropyl and phenyl esters in the 3-phenyltropane series of analogs have higher
affinity for the dopamine transporter than the methyl ester [205]. Similarly, tertiary amide analogs of cocaine and phenyltropane analogs are more potent than secondary or primary amides, and also have enhanced selectivity for binding at the dopamine transporter over the norepinephrine or serotonin transporters [205]. Replacement of the ester or amide function with a substituted carboethoxy isoxazole substituent gave 36, a highly potent inhibitor with selectivity for the dopamine transporter [206,207]. This compound had approximately twice the affinity of cocaine at the DAT.

Similarly, Carroll et al. [208] reported that the 1,2,4-oxadiazoles (e.g., 37) that are biososteres of ester groups, are potent cocaine analogs. Compound 37 had low nanomolar affinity for the dopamine uptake transporter with greater than 100-fold selectivity for the dopamine transporter over the norepinephrine and serotonin transporters.

5.3.4. The Ester Linkage at C(3) In cocaine, the 3α-epimer “allococaine” 38 has considerably reduced activity when compared to cocaine itself [209]. This structural change, however, causes the tropane ring to favor the pseudo-chair, rather than the boat conformation that occurs in natural (−)-3β-cocaine.

It was first reported by Clarke et al. [210] that removal of the ester linkage from cocaine, to give a compound with the phenyl ring directly attached to the tropane ring (WIN 35,065-2; 39), possessed higher affinity for the dopamine transporter than did cocaine itself. By contrast to benzoyl esters, however, the configuration at the 3-position is not so critical in phenyltropane compounds. That is, in the WIN series where the ester has been removed, the 3β-phenyl orientation 39 was only approximately twofold more potent than the 3α-phenyl 40 at the dopamine transporter. At the serotonin transporter, however, the 3β-

5.3.5. Substitutions on the Aromatic Ring at Position 3 In the phenyltropane analogs of cocaine, where the ester linkage has been removed and the phenyl ring is attached directly to the tropane ring (WIN and RTI compounds), substitution at the para ring position with halogens or a methyl group gave compounds (41) with increased affinities at the dopamine transporter compared with the
unsubstituted compound, and with much increased affinity compared to cocaine itself [211]. Behavioral potency paralleled the affinity increases, with all of the phenyltropanes being considerably more potent in elevating locomotor activity in mice [212] and in substituting for a cocaine stimulus in the drug discrimination paradigm in rats [213].

\[
\text{NH}_3\text{C}\\text{OCH}_3
\]

\[X = \text{F, Cl, Br, I, CH}_3\]

The rank order of affinity for aromatic ring substituents in the WIN series was \(3,4\)-Cl\(_2\) > I > Cl > F > H, whereas in the 8-oxa (3\(\beta\)) analogs it was \(3,4\)-Cl\(_2\) > Br > Cl > I > F > H [197]. Replacing the 3\(\beta\)-phenyl with either a 1- or 2-naphthyl substituent gave significantly enhanced affinity at all three monoamine transporters, with the 2-naphthyl 43 being approximately five- to sixfold more potent than the 1-naphthyl 42 [214]. This result parallels similar findings reported by Deutsch et al. [189], where replacing the phenyl ring of methylphenidate with a 2-naphthyl moiety gave an analog with approximately 70-fold higher potency than when the phenyl ring was replaced with a 1-naphthyl.

5.3.6. Requirement for the Intact Tropane Ring System

We have seen earlier that there is no absolute requirement for the basic nitrogen in the tropane structure, and that even a polar oxygen isostere replacement is not required for cocaine congeners to possess potent monoamine reuptake inhibition. It is perhaps not too surprising, therefore, that the bridged bicyclic tropane ring is not an essential structural feature. In a series of 4-arylpiperidine carboxylic acid methyl esters, several of the compounds were significantly better uptake inhibitors than cocaine [215]. The most potent compound in the series, 44, was approximately 20 times more potent than cocaine at the dopamine uptake transporter.

6. RECENT AND FUTURE DEVELOPMENTS

As reviewed above, the drugs that have been used for their stimulant properties were largely the result of compounds that were discovered empirically over many centuries. Understanding the active principles of these drugs has led to major advances in medicinal chemistry. For example, one of the most exciting recent findings has to do with understanding the monoamine transporters at the molecular level. Whereas it has been known in pharmacology for many years that cocaine targeted an energy-dependent reuptake pump, the cloning and expression of these transporters has given access to high “purity” proteins that are amenable to more detailed study. These proteins have all been sequenced, and shown to be membrane bound with twelve membrane-spanning helical segments. A large number of site-specific
mutations have been used to correlate specific residues in the protein with specific functions. A major breakthrough occurred with the solution of the crystal structure of the *Aquifex aeolicus* bacterial leucine transporter in 2005. Since that time, a number of related transporter proteins have been crystallized and their structures determined by X-ray crystallography. Combined with site-directed mutagenesis, cysteine-scanning accessibility methods, high field NMR, homology modeling, and continued development of structure–activity relationships, these advances are now leading to continually improved models of the monoamine transporters. At the moment, these approaches are having the greatest impact on studies of uptake inhibitors, such as antidepressants, rather than studies of substrates.

Particularly interesting recent advances indicate that ligands from different chemical classes may bind in novel ways to the dopamine transporter. Using site-directed mutagenesis and photoaffinity labeling probes, investigators have produced results suggesting that the substrate uptake and cocaine binding sites are probably not identical [216]. Indeed, it also now seems likely that different chemical classes of uptake inhibitors may even bind to distinct regions of the transporter [217,218], leading to different overall conformations in the transporter protein and perhaps subtly altered mechanisms of inhibition. These different transporter conformations would explain the observed differences in the pharmacology of different chemical classes of DAT inhibitors. New derivatives that have selective affinity at these alternate binding sites may block the actions of cocaine without markedly affecting the normal transport function of the protein. Hence, there is presently intense interest in such compounds because they may provide new avenues for the treatment of cocaine and psychostimulant addiction.

There also is a need for improved drugs to replace existing CNS stimulants, as treatments for medical conditions such as narcolepsy, ADHD, obesity, and for general attentional purposes. Yet virtually all of the existing stimulants have the capacity to produce enhanced mood, or euphoria. This side effect means that they all possess abuse potential to a greater or lesser degree. Advances in medicinal chemistry and molecular neurobiology have provided hope, however, for new generations of drugs. For example, the nonamphetamine, nonstimulant drug modafinil (Provigil 45) was recently approved for use in narcolepsy (for example, see Ref. [219]). This drug has been shown to be more effective and have fewer side effects than amphetamine, although its mechanism of action has not yet been fully elucidated. A number of double-blind placebo controlled studies have shown efficacy of modafinil in narcolepsy [220]. Modafinil also has shown efficacy in shift work sleep disorder [221], and there is increasing evidence that modafinil can improve working memory, episodic memory, and processes requiring cognitive control.

Studies with mutant dopamine D₁ and D₂ knockout mice have recently shown that both the D₁ and D₂ receptors are necessary for the wakefulness induced by modafinil [222]. A recent PET study showed significant binding of the DAT and NET, and DAT occupancy comparable to methylphenidate at clinically relevant doses [223]. Modafinil seems to have multiple effects on brain catecholaminergic systems, including NET and DAT inhibition, elevating catecholamines, glutamate, and serotonin, activating the orexinergic system, and decreasing GABA. Alpha-adrenergic, D₁, and D₂ receptors appear to mediate its effects [220].

![Modafinil](image)

The discovery that mutations of either the gene for the novel neuromodulator orexin or the orexin receptor can cause narcolepsy, leads to the hope for even better and more specific drugs to treat that disorder, as well as to the possibility of better treatments for obesity [224–227].

Even those actions of the stimulants that are absolutely dependent on activation of monoamine systems also may be amenable to
breakthroughs in medicinal chemistry. For example, the beneficial effects of stimulants on ADHD may be due primarily to activation of only certain receptors. Recently, the anatomical and functional substrates of attention, learning, and memory have begun to yield their secrets. This work has suggested that certain drugs (e.g., selective D₁ dopamine agonists) [228,229] may provide all or much of the beneficial effects of the stimulants without the abuse potential. Finally, the cracking of the human genome, and the prediction of more than 100,000 human proteins, offers the hope for novel targets for future efforts in medicinal chemistry. Whereas these may be known neurotransmitter pathways (e.g., GABA or glutamate receptors), new targets may be novel proteins whose function is not understood today, but will be tomorrow, and current uses of psychostimulants may be no more than historical artifacts in a decade.

7. WEB SITE ADDRESSES AND RECOMMENDED READING

http://www.mentalhealth.com/
http://www.psyweb.com/indexhtml.html
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28 CNS STIMULANTS


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