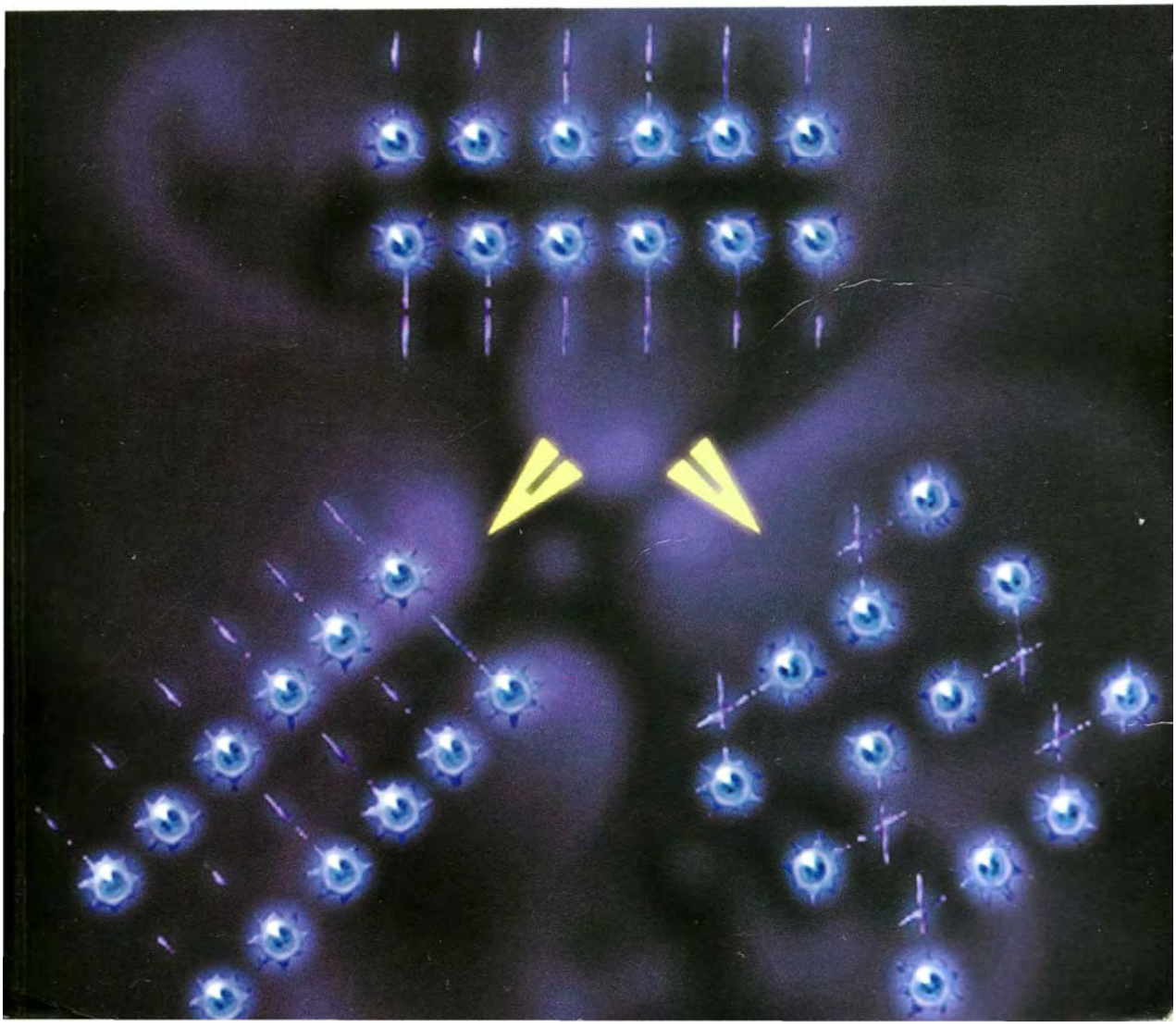
Stephen M. Stahl

Essential Psychopharmacology

Neuroscientific Basis and Practical Applications

Second Edition



ESSENTIAL PSYCHOPHARMACOLOGY

Neuroscientific Basis and Practical Applications
Second Edition

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CONTENTS

CHAPTER 13

PSYCHOPHARMACOLOGY OF REWARD AND DRUGS OF ABUSE

Psychopharmacology is defined in this text as the study of drugs that affect the brain. Until now, all the chapters of this book have addressed how psychotropic drugs affect the brain for therapeutic purposes. Unfortunately, psychotropic drugs can also be abused, and this has caused major public health problems throughout the world. Here we will attempt to explain how abuse of psychotropic agents affects the brain. Our approach to this problem is to discuss how nontherapeutic use, short-term abuse (intoxication), and the complications of long-term abuse affect chemical neurotransmission. We will not discuss the many other important aspects of psychoactive substance abuse, leaving it to other experts to explore such issues as the relationship of drug abuse to economics, criminal behavior, and violence.

Terminology in Psychoactive Substance Use, Abuse, and Reward

Before exploring the neurochemical mechanisms related to psychoactive substance abuse, it is useful to define several terms as they will be used here (Table 13 — 1).

Table 13 — 1. *Nine key terms and their definitions*

Abuse: Self-administration of any drug in a culturally disapproved manner that causes adverse consequences. Addiction: A behavioral pattern of drug abuse characterized by overwhelming involvement with the use of a drug (compulsive use), the securing of its supply, and a high tendency to relapse after discontinuation. Dependence: The physiological state of neuroadaptation produced by repeated administration of a drug, necessitating continued administration to prevent the appearance of the withdrawal syndrome. Reinforcement: The tendency of a pleasure-producing drug to lead to repeated self-administration. Tolerance: Tolerance has developed when after repeated administration, a given dose of a drug produces a decreased effect, or conversely, when increasingly larger doses must be administered to obtain the effects observed with the original use. Cross-tolerance and cross-dependence: The ability of one drug to suppress the manifestations of physical dependence produced by another drug and to maintain the physically dependent state. Withdrawal: The psychologic and physiologic reactions to abrupt cessation of a dependence-producing drug. Relapse: The reoccurrence on discontinuation of an effective medical treatment of the original condition from which the patient suffered. Rebound: The exaggerated expression of the original condition sometimes experienced by patients immediately after cessation of an effective treatment.

Use versus Abuse

Sanctioned uses of drugs have always been defined within a culture and therefore differ across cultures and are prone to change as cultures change over time. When a drug is used in a manner that varies from the use approved by a culture, it is called *abuse.* Therefore, use and abuse of drugs are defined by a culture and not by a psychopharmacological mechanism. *Abuse* is thus defined as the self-administration of any drug in a culturally disapproved manner that causes adverse consequences. It is easier to define and recognize the adverse psychopharmacological consequences of drug self-administration than it is to arrive at a consensus as to what constitutes "cultural disapproval." The purpose of this chapter is not to debate what our culture defines as the line between use and abuse, particularly when that line is blurry. To the brain, it matters little how society defines use versus misuse, and our discussion of the acute actions of psychotropic agents will emphasize how psychopharmacologcal mechanisms are affected in proportion to the *amount* (i.e., dose) of drug being self-administered and the *frequency* of drug self-administration. When the brain's chemical neurotransmission is affected to such a degree that the behavior of individuals takes the form of danger to themselves or others, leading to clinically significant impairment or distress, it is now considered to have passed the threshold of mere use and to qualify for abuse, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) of the American Psychiatric Association.

Reinforcement and reward are the terms that explain in part why individuals repeatedly abuse a drug, namely, the fact that drugs of abuse have various *reinforcing properties,* which cause a pleasure-producing drug to lead to repeated self-

administration. The neurochemical basis of reinforcement is thought to depend on the action of drugs on neurotransmission and is related to what happens in the brain when there is *intoxication* with the drug. Intoxication is a reversible drug-specific syndrome characterized by clinically significant maladaptive behavior or psychological changes that are due to the psychopharmacological actions of the drug on neurotransmission. The symptoms of intoxication range from belligerence to changes in mood to cognitive impairment or impaired judgment to impaired social or occupational functioning.

Addiction, Dependence, Rebound, and Withdrawal

Addiction and dependence are frequently confused. *Addiction* is hard to define, with little consensus on what it means, and in fact is not even defined as a condition in DSM-IV. This term usually refers to a behavioral pattern of drug abuse characterized by overwhelming involvement with use of a drug (compulsive use) and with the securing of its supply and by a high tendency to relapse after discontinuation. *Dependence* is easier to define and will be emphasized in our discussion in this chapter. The term *addiction* is frequently employed by those who are not experts in psycho-pharmacology when *dependence* is what they mean. *Dependence* is a physiological state of neuroadaptation produced by repeated administration of a drug, necessitating continued administration to prevent the appearance of a withdrawal syndrome. Several things can occur when a drug causes dependence and the individual continues taking it, namely, *cross-dependence, tolerance,* and *cross-tolerance.* Several other things can occur when a drug causes dependence and the individual abruptly stops taking it, namely, *withdrawal* and *rebound,* both defined below. Later, in relationship to specific drugs, the various neuroadaptive mechanisms that mediate each of these effects will also be discussed in terms of the impact that they have on chemical transmission of specific neurotransmitters.

Tolerance develops when after repeated administration, a given dose of a drug produces a decreased effect, or conversely, when increasingly larger doses must be administered to obtain the effects observed with the original use. Related to this are *cross-tolerance* and *cross-dependence,* which are the ability of one drug to suppress the manifestations of physical dependence produced by another drug and to maintain the physically dependent state. *Withdrawal* is the term for the adverse psychological and physiological reactions to abrupt cessation of a dependence-producing drug. It is very important to distinguish withdrawal from *rebound,* which are frequently confused, because both are related to the neurochemical changes that mediate dependence. *Rebound* is what happens when tolerance occurs in patients who have taken a drug (usually for a medically sanctioned use), which then is suddenly stopped— their symptoms come back in an exaggerated fashion. *Withdrawal,* on the other hand, is what happens when tolerance occurs in those who have taken a drug (either for abuse or for medically sanctioned use) and then that drug is suddenly stopped— they develop a withdrawal syndrome characterized by craving, dysphoria, and signs of sympathetic nervous system overactivity.

Dependence is a term that is not frequently used outside of psychopharmacology but in fact is a key feature of many antihypertensive medications, hormones, and other treatments throughout medicine. Thus, several antihypertensives can produce *rebound* hypertension, worse than the original blood pressure elevation, when sud-

denly discontinued. These patients are not "addicted" to their blood pressure medications although they are dependent on them. Such hypertensive patients who suddenly discontinue these antihypertensive drugs do not experience withdrawal effects, since their symptoms are an exaggerated manifestation of their original condition, and not a new set of symptoms such as craving and dysphoria. A panic disorder patient who suddenly stops a benzodiazepine and then has rebound panic attacks may be incorrectly accused of being "addicted" to benzodiazepines. As in the case of the patient discontinuing antihypertensives, this panic patient is dependent on his or her medication and experiencing rebound, not withdrawal or addiction. These distinctions among dependence, addiction, rebound, and withdrawal should be kept in mind when educating patients about their medications associated with these actions.

Detoxification

Detoxification is the slow tapering of a drug that has caused dependence and would cause withdrawal if stopped too suddenly. Detoxification can be accomplished either by slowly withdrawing the dependence-forming drug itself or by substitution of a cross-dependent drug that has a similar pharmacological mechanism of action. In either case, detoxification is done by slowly tapering the dependent or cross-dependent drug so that the neuroadaptational mechanisms of dependence can readapt during dose tapering and thus prevent withdrawal symptoms. Tapering of a drug treatment for a medical condition (such as hypertension or panic) that has caused dependence can also prevent the emergence of rebound. In this case, it is not called detoxification but tapered discontinuation. Detoxification generally implies a method to prevent withdrawal, not to prevent rebound.

Rebound versus Relapse

Another important distinction to make is that between *rebound* and *relapse,* as these two terms are constantly confused. The term *relapse* was already introduced in our discussion of depression in Chapter 5. Relapse refers to the reoccurrence of disease symptoms on discontinuation of an effective medical treatment. Relapse assumes an underlying medical condition for which the drug was administered and therefore a medically sanctioned use. Thus, if patients with diabetes mellitus require insulin, they are generally referred to as insulin-dependent, not addicted to insulin. If such patients suddenly stop their insulin, glucose will generally return to pretreatment levels, that is, *relapse* of diabetes, not *rebound* to a worse state of diabetes. Panic patients who require benzodiazepines to suppress panic attacks can similarly be referred to a benzodiazepine-dependent, not addicted to benzodiazepines. If such patients suddenly stop benzodiazepines, they may experience *rebound* panic attacks, i.e., panic attacks that are more frequent and severe than those of the original panic disorder. On discontinuation of benzodiazepines, especially if they are tapered over a long period of time, these patients may very well experience the return of their usual panic attacks, that is, *relapse* of panic disorder. These patients have not developed withdrawal symptoms just because they experience panic attacks after discontinuing benzodiazepines. However, if they develop insomnia, irritability, seizures,

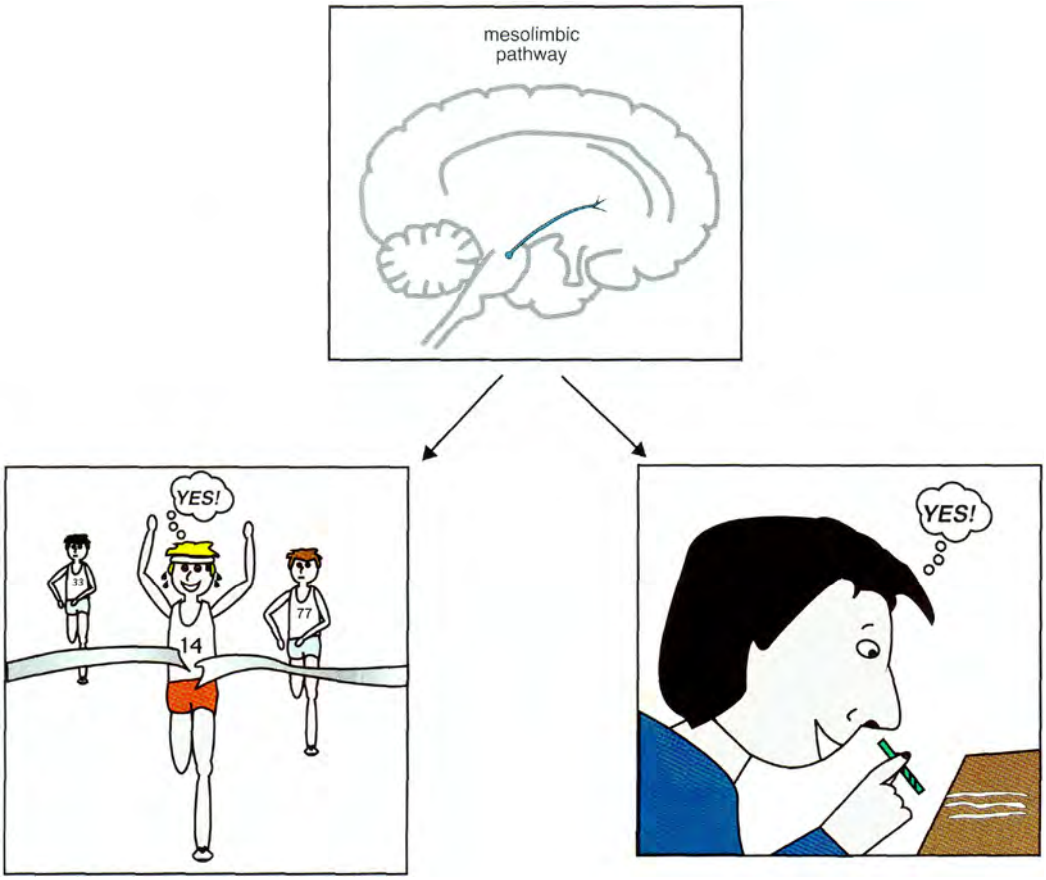


FIGURE 13 — 1. The **mesolimbic dopamine pathway** mediates the **psychopharmacology of reward**, whether that is a natural high or a drug-induced high.

and agitation, none of which were symptoms of their original panic attacks, they *have* developed symptoms of *withdrawal.*

Mesolimbic Dopamine Pathway and the Psychopharmacology of Reward

The final common pathway of reinforcement and reward in the brain is hypothesized to be the mesolimbic dopamine pathway (Fig. 13 — 1). Some even consider this to be the "pleasure center" of the brain and dopamine to be the "pleasure neurotransmitter." There are many natural ways to trigger mesolimbic dopamine neurons to release dopamine, ranging from intellectual accomplishments to athletic accomplishments to enjoying a symphony to experiencing an orgasm. These are sometimes called "natural highs" (Fig. 13 — 1). The inputs to the mesolimbic pathway that mediate these natural highs include a most incredible "pharmacy" of naturally occurring substances, ranging from the brain's own morphine/heroin (endorphins) to

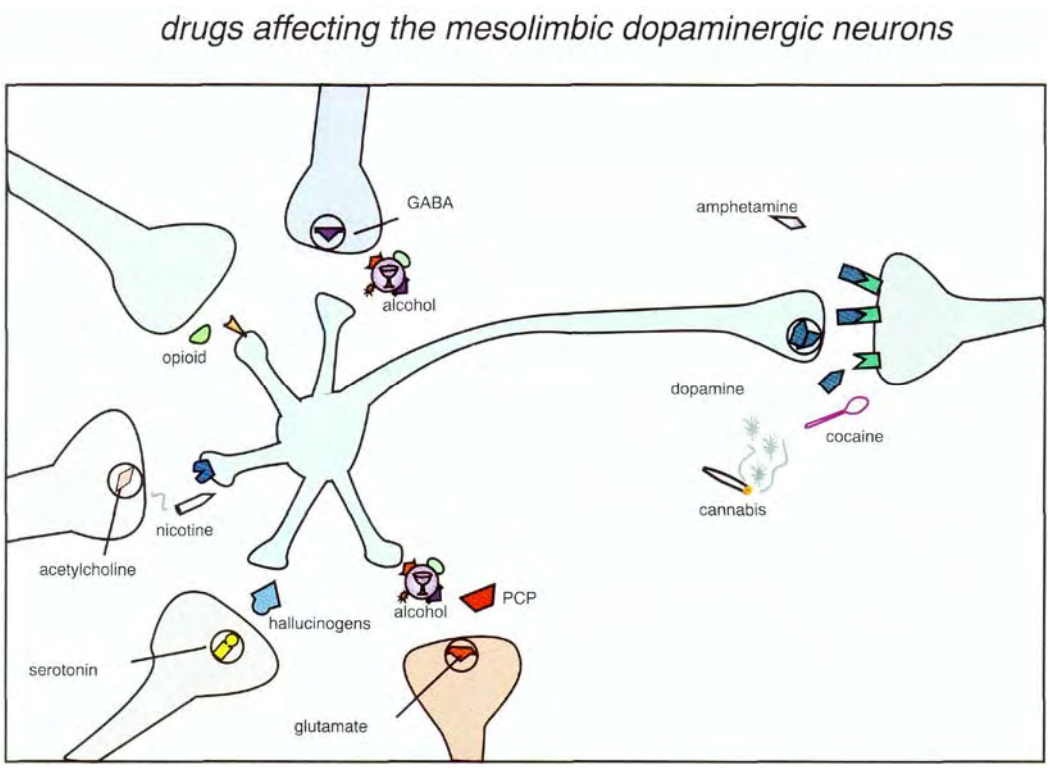


FIGURE 13 — 2. **Mesolimbic dopamine pathway and the psychopharmacology of reward**. The final common pathway of reward in the brain is hypothesized to be the mesolimbic dopamine pathway. The inputs to this pathway include an incredible "pharmacy" of naturally occurring substances, ranging from the brain's own morphine/heroin (i.e., endorphins) to the brain's own marijuana (i.e., anan-damide), to the brain's own cocaine/amphetamine (i.e., dopamine itself). The numerous psychotropic drugs of abuse that occur in nature bypass the brain's own neurotransmitters and directly stimulate the brain's receptors, causing dopamine to be released. Since the brain already uses neurotransmitters that resemble drugs of abuse, it is not necessary to earn the reward naturally, since an artificial "high" can also be obtained on demand. Unfortunately, this can lead to complications. Thus, alcohol, opiates, stimulants, marijuana, benzodiazepines, sedative-hypnotics, hallucinogens, and nicotine all have an impact on this mesolimbic dopaminergic system.

the brain's own marijuana (anandamide), to the brain's own nicotine (acetylcholine), to the brain's own cocaine and amphetamine (dopamine itself) (Fig. 13 — 2).

The numerous psychotropic drugs of abuse that occur in nature also have a final common pathway of causing the mesolimbic pathway to release dopamine, often in a manner more explosive and pleasurable than that which occurs naturally. These drugs bypass the brain's own neurotransmitters and directly stimulate the brain's own receptors for these drugs, causing dopamine to be released (Fig. 13 — 2). Since the brain already uses neurotransmitters that resemble drugs of abuse, it is not necessary to earn one's reward naturally, since a much more intense reward can be obtained in the short run and on demand from a drug of abuse than from a natural high with the brain's natural system. However, unlike a natural high, a drug-induced reward causes such wonderful feeding of dopamine to postsynaptic limbic dopamine

2 (D2) sites that they furiously crave even more drug to replenish dopamine once the drug stops working, leading the individual to be preoccupied with finding more drug and thus beginning a vicious circle.

Because there appears to be an optimal range in which D2 receptor stimulation by the mesolimbic dopamine system is reinforcing, the risk of becoming a substance abuser may depend on how many receptors a person has. Thus, in subjects who have only a few receptors for a given substance, taking that substance will not cause much of an effect at first, but the substance will become more and more rewarding as the dose increases. However, in subjects with many receptors for a given substance, taking that substance will be aversive and they will not want to try it again. One might also postulate that in those with few substance receptors, their own internal reward system is not working too well in the first place. This might predispose them to keep trying drugs as a means of compensating for their own naturally decreased activation of reward circuits. In fact, studies in alcoholics, cocaine abusers, and amphetamine abusers show that a low initial response to a drug predicts a high risk for ultimate abuse, whereas a high initial response to a drug predicts a low risk of abuse.

Stimulants: Cocaine and Amphetamine

Cocaine (Fig. 13 — 3) has two major properties: it is both a local anesthetic and an inhibitor of monoamine transporters, especially dopamine (Fig. 13-4). Cocaine's local anesthetic properties are still used in medicine, especially by ear, nose, and throat specialists (otolaryngologists). Freud himself exploited this property of cocaine to help dull the pain of his tongue cancer. He may have also exploited the second property of the drug, which is to produce euphoria, reduce fatigue, and create a sense of mental acuity due to inhibition of dopamine reuptake at the dopamine transporter. Cocaine also has similar but less important actions at the norepinephrine and the serotonin transporters (Fig. 13 — 3). Cocaine may do more than merely block the transporter—it may actually release dopamine (or norepinephrine or serotonin) by reversing neurotransmitter out of the presynaptic neuron via the monoamine transporters (Fig. 13—4).

At higher doses, cocaine can produce undesirable effects, including tremor, emotional lability, restlessness, irritability, paranoia, panic, and repetitive stereotyped behavior. At even higher doses, it can induce intense anxiety, paranoia, and hallucinations, along with hypertension, tachycardia, ventricular irritability, hyperther-mia, and respiratory depression. In overdose, cocaine can cause acute heart failure, stroke, and seizures. Acute intoxication with cocaine produces these various clinical effects, depending on the dose; these effects are mediated by inhibition of the dopamine transporter and in turn by the effects of excessive dopamine activity in dopamine synapses, as well as by norepinephrine and serotonin in their respective synapses.

Repeated intoxication with cocaine may produce complex adaptations of the dopamine neuronal system, including both tolerance and, indeed, the opposite phenomenon, called sensitization or *reverse tolerance.* One example of reverse tolerance may be what happens to some abusers on repeated intoxication with cocaine at doses that previously only induced euphoria. In these cases, cocaine causes a behavioral

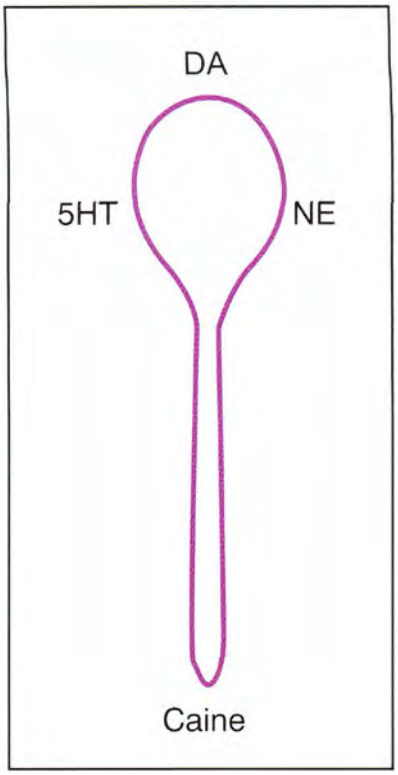


FIGURE 13 — 3. Icon of **cocaine**. The main mechanism of action is to block reuptake and cause the release of monoamines, principally dopamine (DA), but also norepinephrine (NE) and serotonin (5HT). There is also a local anesthetic action (caine).

reaction that can take the form of an acute paranoid psychosis virtually indistinguishable from paranoid schizophrenia (Fig. 13 — 5).

This should not be surprising, because the major hypothesis for the etiology of the positive symptoms of psychosis (discussed in Chapter 10 on schizophrenia) is an excess of dopamine activity in this same mesolimbic dopamine pathway (see Fig. 10 — 9). When the reinforcing properties of cocaine, mediated via mild to moderate stimulation of D2 receptors in this pathway, become "too much of a good thing" (i.e., the compulsive quest for euphoria and pleasure through pleasurable stimulation of these receptors), this eventually results in sensitization of these receptors and induction of *overactivity* in this pathway, reproducing the pathophysiology underlying the positive symptoms of schizophrenia (see Fig. 10—9). This complication of cocaine abuse requires chronic use in order to sensitize the mesolimbic dopamine system, which eventually releases progressively more and more dopamine until repetitive cocaine abuse erupts into frank psychosis. How the dopamine synapse becomes sensitized to cocaine so that this effect can be produced on repeated administration is unknown. Interestingly, treatment with dopamine receptor-blocking atypical antipsychotics or conventional antipsychotics can also relieve the symptoms of cocaine intoxication, as would be expected by analogy with schizophrenia (see Fig. 11-2).

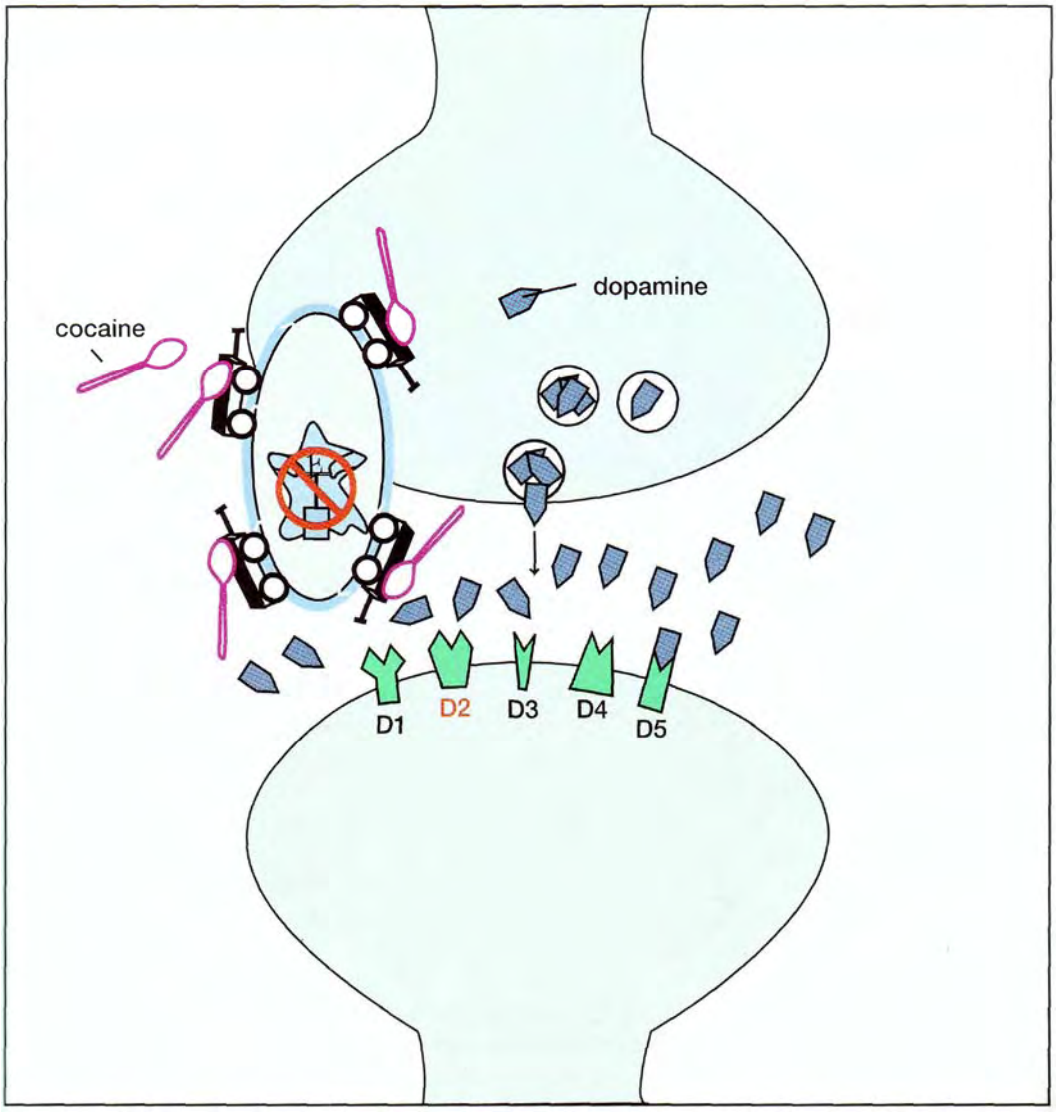


FIGURE 13—4. *Pharmacology of cocaine.* Cocaine is a powerful inhibitor of the dopamine transporter. Blocking this transporter acutely causes dopamine to accumulate, and this produces euphoria, reduces fatigue, and creates a sense of mental acuity. Cocaine has similar but less important actions at the norepinephrine and serotonin transporters.

In addition to the acute intoxicating effects and the chronic reverse tolerance effects of cocaine, all of which are mediated by increasing dopamine levels due to its release from dopamine synapses, there are also longer-term effects of cocaine, possibly due to other, more traditional desensitization types of adaptations of dopamine receptors. As abusers use cocaine for longer and longer periods of time, their dopamine receptors become desensitized (down-regulated) as they adapt to chronic

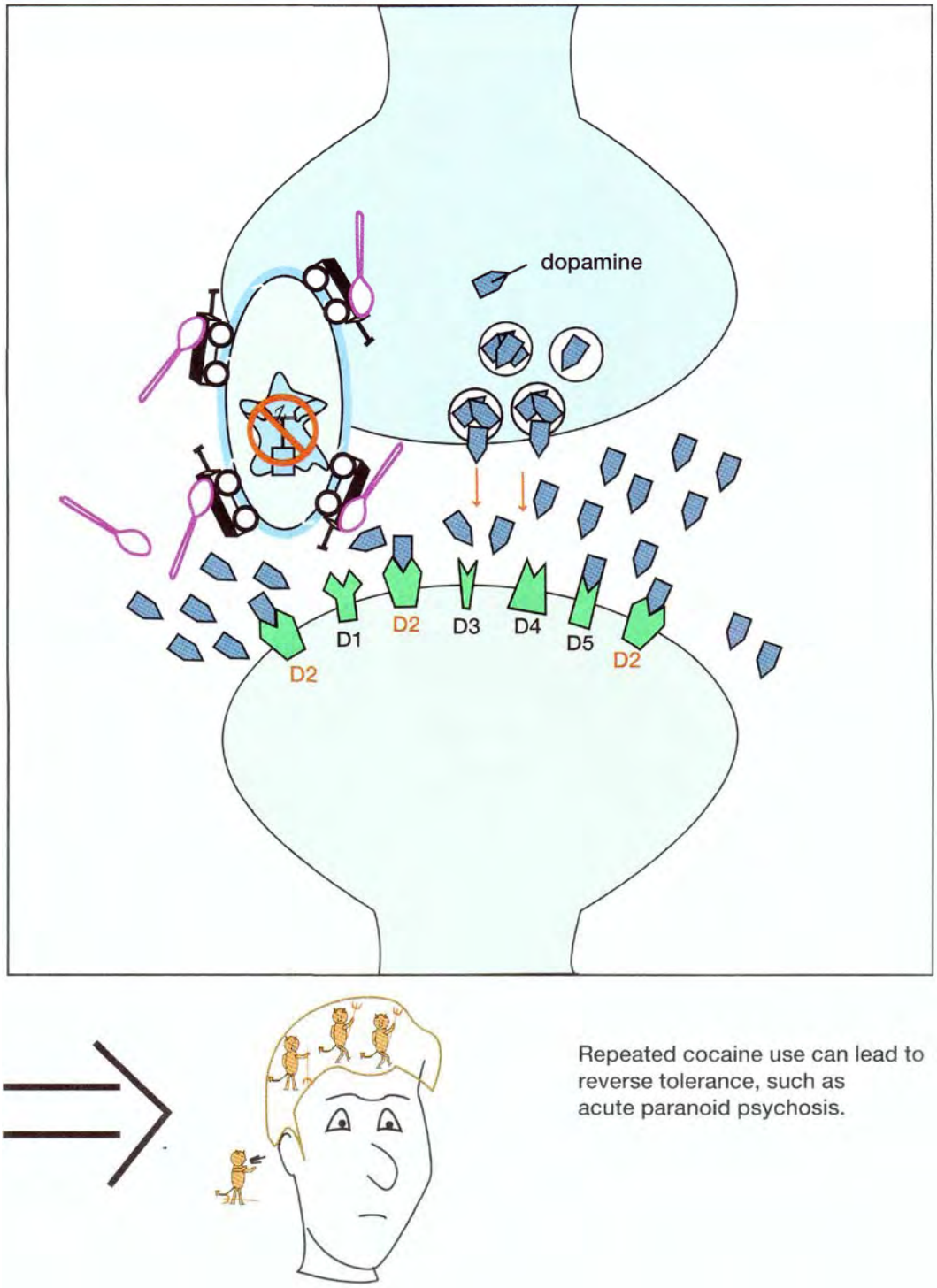


FIGURE 13 — 5. *Production of reverse tolerance in a cocaine abuser.* Repeated intoxication with cocaine may produce complex adaptations of the dopamine neuronal system, such as sensitization or "reverse tolerance." Thus, in repeat users, cocaine releases more and more dopamine. In such cases doses of cocaine that previously only induced euphoria can create an acute paranoid psychosis virtually indistinguishable from paranoid schizophrenia.

exposure. After consecutive episodes of intoxication followed by abstinence, they mediate an increasingly bothersome withdrawal syndrome.

A subjective experience that may follow the euphoria is a sense of "crashing," characterized by craving more cocaine and accompanied by agitation and anxiety, giving way to fatigue, depression, exhaustion, hypersomnolence, and hyperphagia. After several days, if another dose of cocaine is not taken, the chronic abuser may experience other signs of withdrawal, including anergy, decreased interest, anhedonia, and increased cocaine craving.

Since dopamine neurotransmission via D2 receptors in the mesolimbic dopamine pathway is thought to mediate in large part the psychopharmacology of pleasure and therefore the reinforcing properties of many drugs of abuse, it is not surprising that cocaine abusers describe their highs as more intense and pleasurable than orgasm and their lows as the inability to experience any pleasure whatsoever (anhedonia). These latter complaints are reminiscent of symptoms of depression, and it is not surprising that a condition that acts to mobilize and deplete dopamine and then to desensitize dopamine receptors could create a condition that mimics the signs of major depressive disorder. Interventions aimed at repleting dopamine stores and readapting dopamine receptor sensitivity would be theoretically useful for the cocaine abuser dependent—with both tolerance and reverse tolerance—on cocaine. However, the most useful intervention often is to allow the dopamine system to restore itself with time alone, provided that the abuser can remain abstinent long enough for the system to recover. This, of course is often not feasible or even desired by the abuser. In the future, there may be a "reverse cocaine" available for therapeutic purposes, which would work analogously to the action of a "reverse serotonin selective reuptake inhibitor (SSRI)" or "serotonin reuptake enhancer" tianeptine, as discussed in the section on the mechanism of action of the SSRIs in Chapter 6. This experimental agent for cocaine abuse does not block the reuptake pump for dopamine, nor does it cause a reverse flow of dopamine out of the synapse, as does cocaine; it actually pumps dopamine back into the presynaptic neuron, and is thus a dopamine reuptake enhancer. Another therapeutic possibility for cocaine abusers in the future would be antibodies to cocaine.

Amphetamines, especially *d-ampbetamine* and *methampbetamine* (Fig. 13—6), also have potent pharmacological effects on the dopamine neuron. Their predominant actions are to release dopamine (Figs. 13—7 and 13 — 8). Amphetamine and derivatives of amphetamines also have weaker releasing actions at noradrenergic synapses as discussed in Chapter 12 (see Figs. 12—4 and 12 — 5), and some amphetamine derivatives also release serotonin. Recently, a new neurotransmitter system, called cocaine- and amphetamine-regulated transcript (CART) peptides, has been discovered. This is a peptide neurotransmitter system, identified first as mRNA (i.e., a transcript) that was increased after administration of either cocaine or amphetamine. Now that the peptides for which this RNA codes are being characterized, it appears that these so-called CART peptides probably have a role in drug abuse and in the control of stress and feeding behavior. Their receptors could be a target for future drug abuse therapies.

The clinical effects of amphetamine and its derivatives are very similar to those of cocaine, although the euphoria they produces may be less intense but last longer than that due to cocaine. Signs of amphetamine intoxication, toxicity, overdose, sensitization by production of an acute paranoid psychosis, and withdrawal syndrome are all similar to those described above for cocaine.

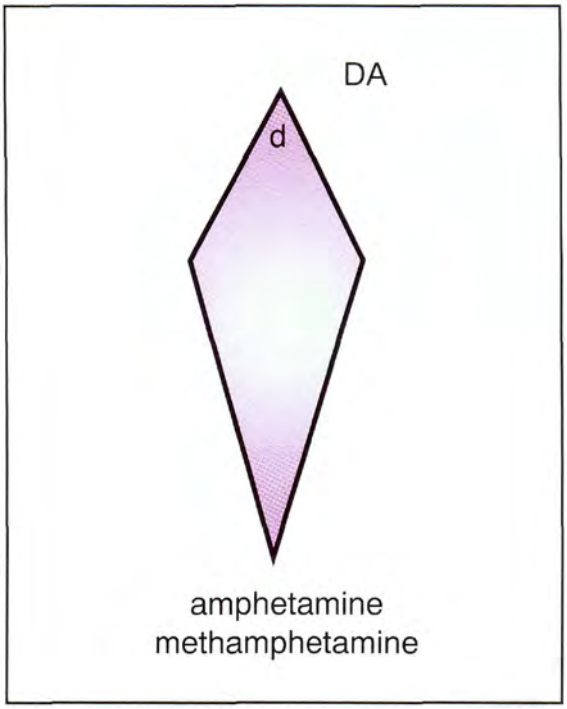


FIGURE 13 — 6. Icon of **amphetamine/methamphetamine**. Amphetamine (principally *d*-amphetamine) and related derivatives such as methamphetamine are also releasers of dopamine, with a mechanism similar to that described for cocaine.

Hallucinogens, Designer Drugs, and Phencyclidine

Hallucinogens

The hallucinogens are a group of agents that produce intoxication, sometimes called a "trip," associated with changes in sensory experiences, including visual illusions and hallucinations, an enhanced awareness of external stimuli, and an enhanced awareness of internal thoughts and stimuli. These hallucinations are produced with a clear level of consciousness and a lack of confusion and may be both psychedelic and psychotomimetic. *Psychedelic* is the term for the subjective experience, due to heightened sensory awareness, that one's mind is being expanded or that one is in unison with mankind or the universe and having some sort of a religious experience. *Psychotomimetic* means that the experience mimics a state of psychosis (see Table 10—3), but the resemblance between a trip and psychosis is superficial at best. As previously discussed, the stimulants cocaine and amphetamine mimic psychosis much more genuinely.

Hallucinogen intoxication includes visual illusions; visual "trails," in which the image smears into streaks as it moves across a trail; macropsia and micropsia; emotional and mood lability; subjective slowing of time; the sense that colors are heard and sounds are seen; intensification of sound perception; depersonalization and de-realization. All these effects may be experienced while yet retaining a state of full wakefulness and alertness. Other changes may include impaired judgment, fear of

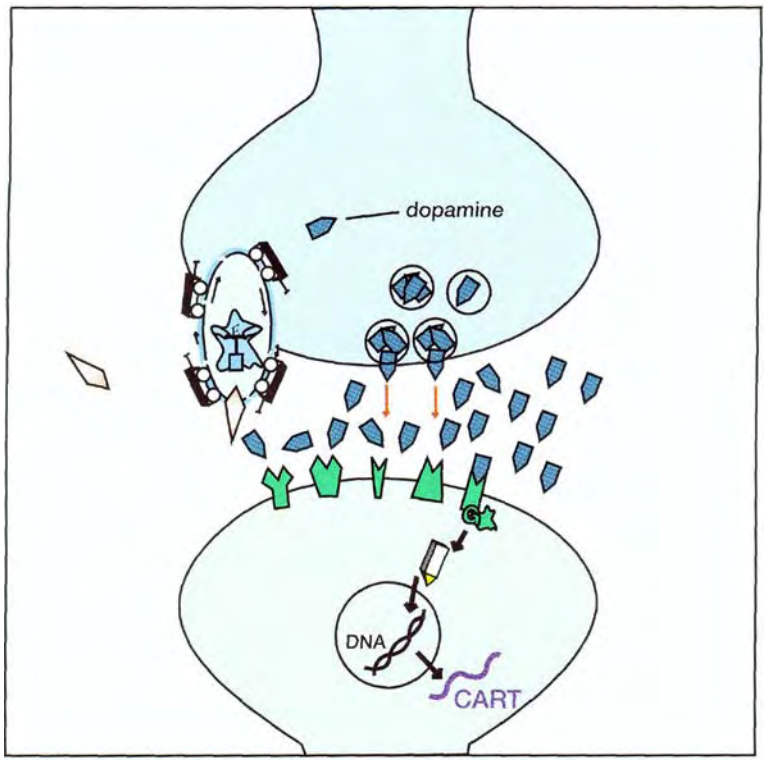


FIGURE 13 — 7. *Pharmacology of amphetamine (part 1).* It has recently been discovered that after amphetamine releases dopamine, the postsynaptic targets of amphetamine stimulate the expression of some novel genes, which make messenger RNA for a novel neurotransmitter system. The messenger RNA (or transcript) is called cocaine- and amphetamine-regulated transcript (CART) (see Fig.13-8). CART is a novel neurotransmitter system, which may be involved in regulating neuronal systems in drug abuse.

losing one's mind, anxiety, nausea, tachycardia, increased blood pressure, and increased body temperature. Not surprisingly, when the list of symptoms above is compared with the list of symptoms for a panic attack in Chapter 9 (Table 9 — 6), hallucinogen intoxication can cause what is perceived as a panic attack but often called a "bad trip." As intoxication escalates, one can experience an acute confusional state called *delirium*, in which the abuser is disoriented and agitated. This can evolve further into frank psychosis with delusions and paranoia.

Common hallucinogens include two major classes of agents. Agents of the first class (indolealkylamines) resemble serotonin and include the classical hallucinogens *d*-lysergic acid diethylamide (LSD), psilocybin, and dimethyltryptamine (DMT) (Fig. 13—9). Agents of the second class (phenylalkylamines) resemble norepinephrine and dopamine, are also related to amphetamine, and include mescaline, 2,5-dimethoxy-4-methylamphetamine (DOM), and others. More recently, synthetic chemists have come up with some new "designer drugs" such as 3,4-methylenedioxymethamphetamine (MDMA). These are either stimulants or hallucinogens and produce a complex subjective state sometimes referred to as "ecstasy," which is also what abus-

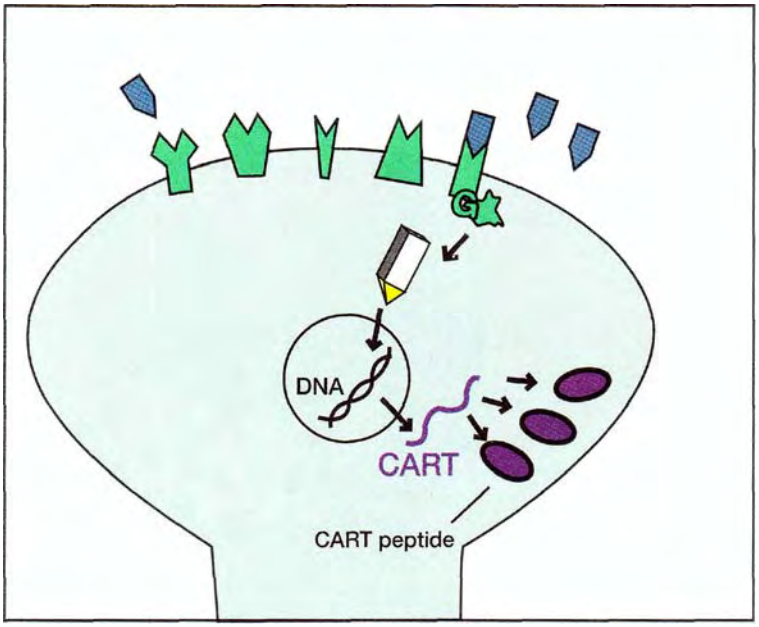


FIGURE 13 — 8. *Pharmacology of amphetamine (part 2).* After dopamine is released and the postsynaptic target cells express genes for cocaine- and amphetamine-regulated transcript (CART) as shown in Figure 13-7, the next step is the synthesis of various neurotransmitter CART peptides. These peptides probably have a role not only in drug abuse but also in the control of stress and feeding behavior. Their receptors could be targets for future drug abuse therapies.

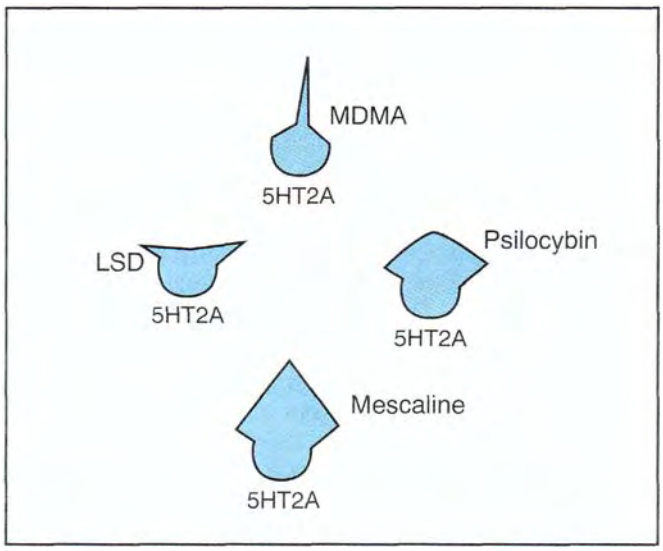


FIGURE 13—9. Icons of **hallucinogens**. Hallucinogens such as lysergic acid diethylamide (LSD), mescaline, psyloscibin, and 3,4-methylenedioxymethamphetamine (MDMA) are partial agonists at 5HT2A receptors.

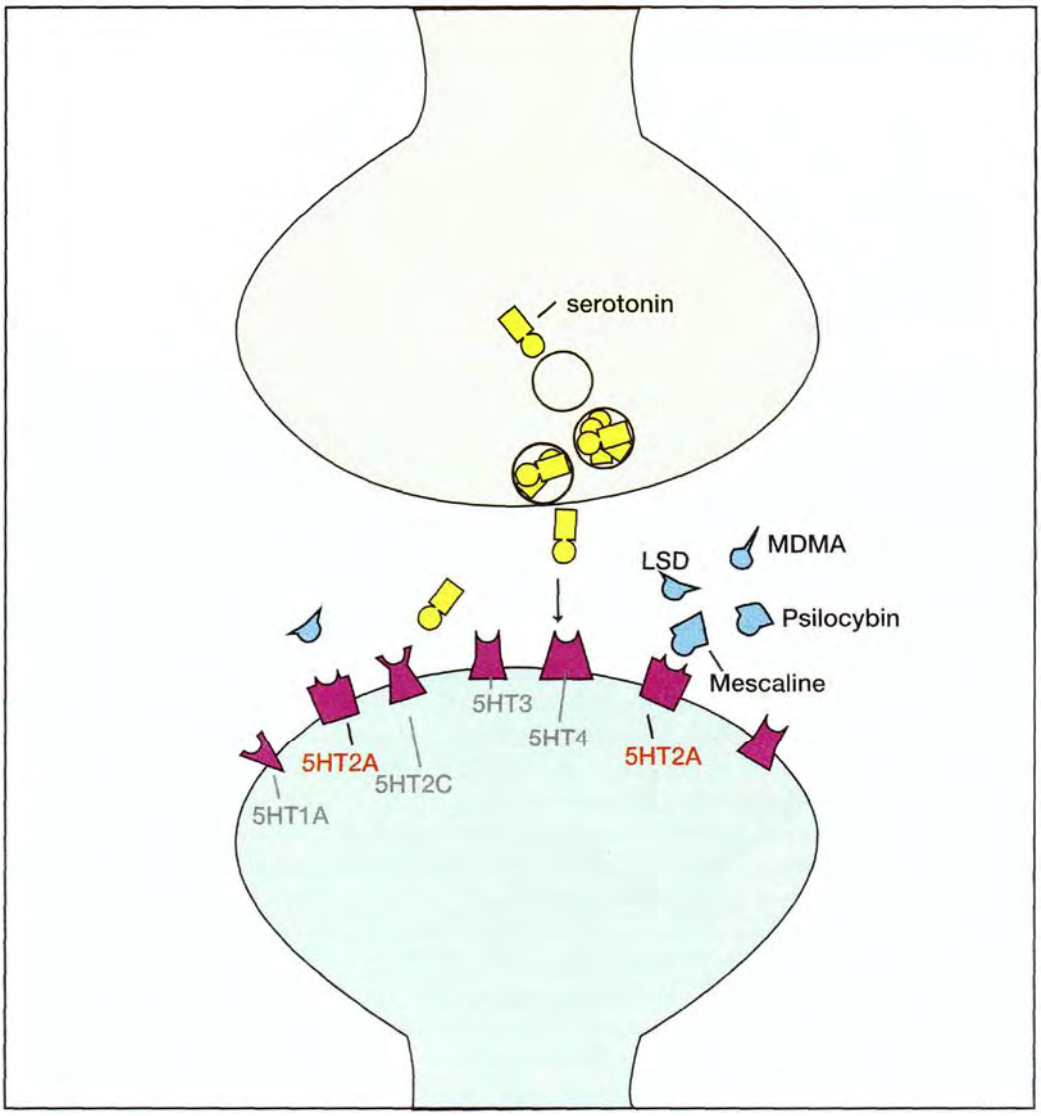


FIGURE 13 — 10. Here hallucinogenic drugs such as LSD, mescaline, and psilocybin, as well as the "designer drugs" such as MDMA, are interacting as partial agonists at 5HT2A receptors at serotoninergic postsynaptic neuronal sites.

ers call MDMA itself. The effects of MDMA include euphoria, disorientation, confusion, enhanced sociability, and a sense of increased empathy and personal insight. Hallucinogens have rather complex interactions at neurotransmitter systems, but one of the most prominent is a common action as agonists at serotonin 2A (5HT2A) receptor sites (Fig. 13 — 10). Hallucinogens certainly have additional effects at other 5HT receptors (especially 5HT1A somatodendritic autoreceptors) and also at other neurotransmitter systems, especially norepinephrine and dopamine, but the relative importance of these other actions are less well known. Also, MDMA appears to be a powerful releaser of serotonin and it and several drugs structurally related to it

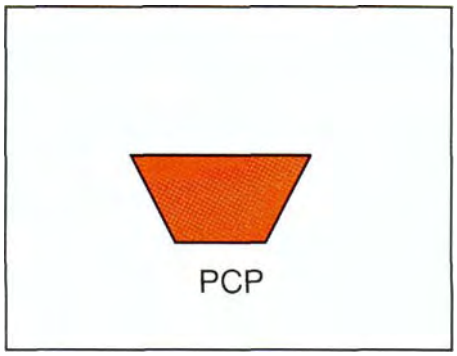


FIGURE 13 — 11. Icon of **phencyclidine** (**PCP**). Phencyclidine is an antagonist of an ion channel site associated with the N-methyl-*d*-aspartate (NMDA) subtype of glutamate receptor.

may even destroy serotonin axon terminals. However, the action that appears to explain a common mechanism for most of the hallucinogens is the stimulation of 5HT2A receptors.

Hallucinogens can produce incredible tolerance, sometimes after a single dose. Desensitization of 5HT2A receptors is hypothesized to underlie this rapid clinical and pharmacological tolerance. Another unique dimension of hallucinogen abuse is the production of "flashbacks," namely the spontaneous recurrence of some of the symptoms of intoxication, which lasts from a few seconds to several hours but in the absence of recent administration of the hallucinogen. This may occur days to months after the last drug experience and can apparently be precipitated by a number of environmental stimuli. The psychopharmacological mechanism underlying flashbacks is unknown, but its phenomenology suggests the possibility of a neurochem-ical adaptation of the serotonin system and its receptors related to reverse tolerance and incredibly long-lasting. Alternatively, flashbacks could be a form of emotional conditioning triggered when a later emotional experience occurring when one is not taking a hallucinogen nevertheless reminds one of experiences that occurred when intoxicated with a hallucinogen. This could precipitate a whole cascade of feelings that occurred originally while intoxicated with a hallucinogen. This is analogous to the reexperiencing flashbacks that occur without drugs in patients with posttrau-matic stress disorder.

Phencyclidine

Phenylcyclidine (PCP) (Fig. 13 —11) was originally developed as an anesthetic but proved to be unacceptable for this use because it induces a unique psychotomimetic-hallucinatory experience. Its structurally related and mechanism-related analogue ketamine is still used as an anesthetic but causes far less of the psychotomimetic-hallucinatory experience. Nevertheless, some people do abuse ketamine, one of the "club drugs," which is sometimes called "special K." Phenylcyclidine causes intense analgesia, amnesia, delirium, stimulant as well as depressant effects, staggering gait, slurred speech, and a unique form of nystagmus (i.e., vertical nystagmus). Higher degrees of intoxication can cause catatonia (excitement alternating with stupor and catalepsy), hallucinations, delusions, paranoia, disorientation, and lack of judgment.

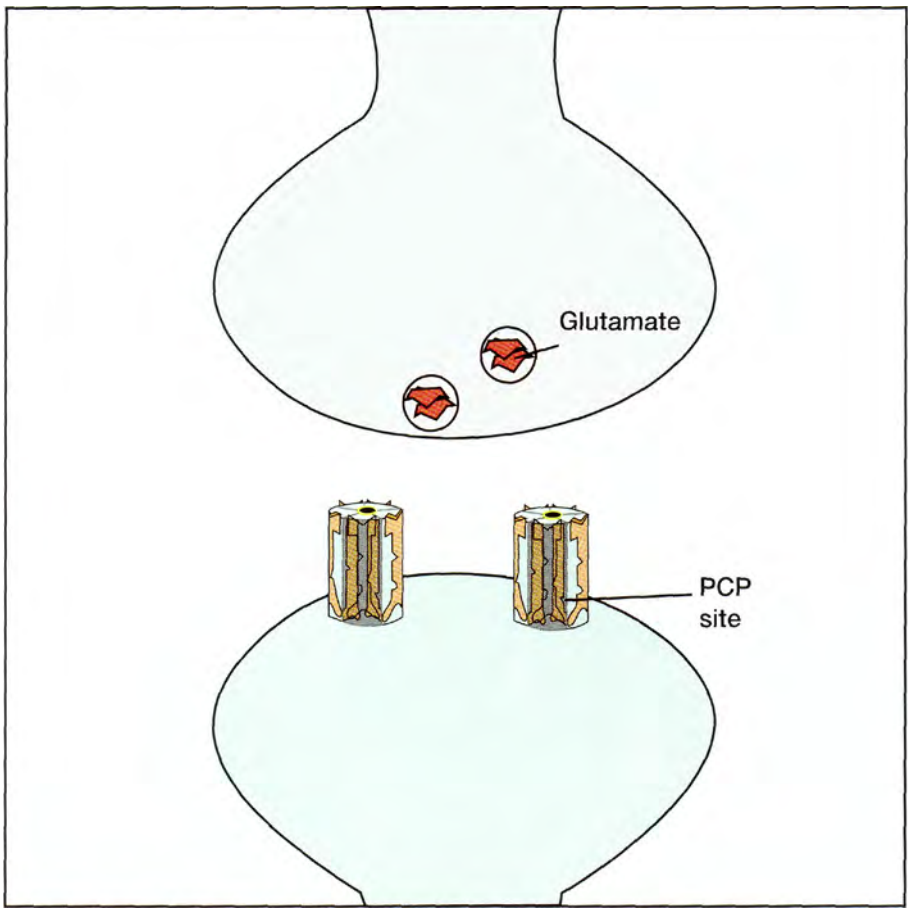


FIGURE 13 — 12. *Pharmacology of phencyclidine (PCP).* Phenylcyclidine is an open-channel *antagonist of N-methyl-d-aspartate (NMDA) glutamate receptors* at a site probably closely associated with the calcium ion channel there. This means that its site is probably inside the calcium channel, and it probably works best when the channel is open.

Overdose can include coma, extremely high temperature, seizures, and muscle breakdown (rhabdomyolysis).

We have already briefly mentioned the mechanism of action of PCP in Chapter 10 in our discussion on neuroprotective agents (Fig. 10 — 24). It acts as an allosteric modulator of the NMDA subtype of glutamate receptor (Figs. 13 — 12 and 13 — 13). It specifically acts to block this receptor and to decrease the flux of calcium into the cell. Phenylcyclidine itself and other agents that act at the PCP receptor may be neuroprotective, but apparently only at the expense of disrupting memory and causing psychosis (Fig. 13 — 13).

Getting Stoned With or Without Inhaling: Marijuana and the Endocannabinoids

Cannabis preparations are smoked in order to deliver their psychoactive substances, cannabinoids, especially THC delta-9-tetrahydrocannabinol (THC) (Fig. 13 — 14).

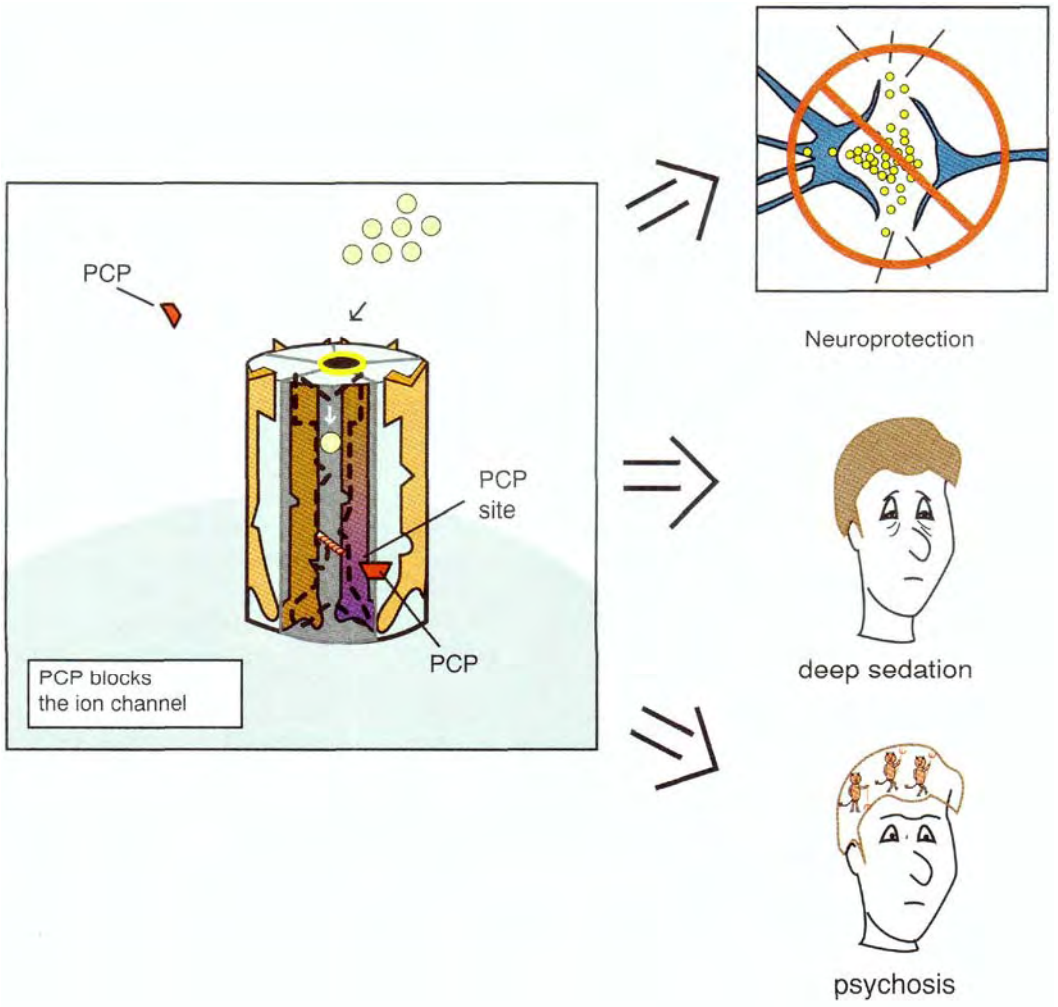


FIGURE 13 — 13. The PCP site is a modulatory site for the ion channel at the NMDA glutamate receptor—calcium channel complex, which can block this channel and prevent calcium from flowing through it in response to glutamate. This can be neuroprotective at very high doses and sedating or anesthetic at high doses but psychotomimetic at moderate doses.

These smoked substances interact with the brain's own cannabinoid receptors to trigger dopamine release from the mesolimbic reward system. There are two known cannabinoid receptors, CB1 (in the brain, which is coupled via G proteins and modulates adenylate cyclase and ion channels) and CB2 (in the immune system). The CB1 receptors may mediate not only marijuana's reinforcing properties, but also those of alcohol. There is also an endogenous cannabinoid system (the brain's own marijuana) capable of activating these cannabinoid receptors functionally. These *endocannabinoids* are synthesized by neurons and inactivated by reuptake systems and enzymes in both neurons and glia.

Anandamide is one of these endocannabinoids and a member of a new chemical class of neurotransmitters, which is not a monoamine, not an amino acid, and not

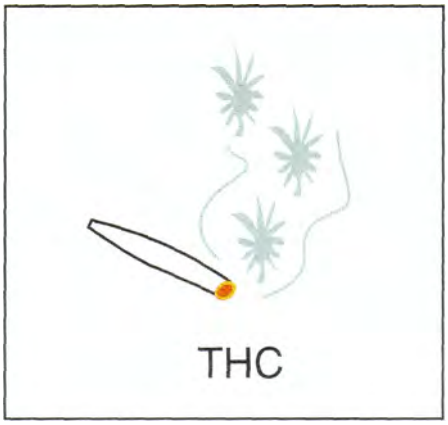


FIGURE 13 — 14. Icon for **tetrahydrocannabinol** (**THC**), the psychoactive ingredient in marijuana.

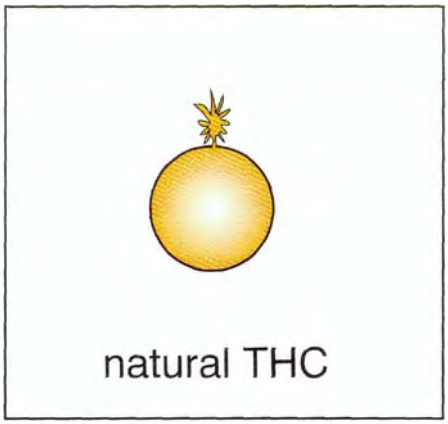


FIGURE 13 — 15. Icon for **anandamide**, the brain's endocannabinoid (the "brain's own marijuana").

a peptide—it is a lipid, specifically a member of a family of fatty acid ethanolamides (Fig. 13 — 15). Anandamide shares most but not all of the pharmacologic properties of THC, since its actions at brain cannabinoid receptors are not only mimicked by THC but are antagonized in part by the selective brain cannabinoid antagonist SR141716A (Fig. 13 — 16). The discovery of this marijuana antagonist (Fig. 13 — 16) opens the door to using it as a potential therapeutic agent in various types of drug abuse. It is already in clinical testing in schizophrenia (as discussed in Chapter 11), since that disorder is hypothesized to be due to hyperactivity in the same pathway that mediates reward (Fig. 10 — 9) and is overstimulated by drugs of abuse (Fig. 13-2).

Marijuana can have both stimulant and sedative properties. In usual intoxicating doses, it produces a sense of well-being, relaxation, and friendliness, a loss of temporal awareness, (including confusing the past with the present), slowing of thought processes, impairment of short-term memory, and a feeling of achieving special insights. At high doses, marijuana can induce panic, toxic delirium, and rarely, psy-

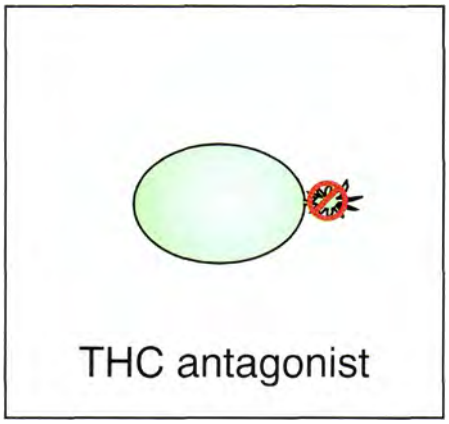


FIGURE 13 — 16. Icon for **marijuana antagonist**, theoretically a treatment for drug abuse and for use in testing for schizophrenia.

chosis. One complication of long-term use is the so-called amotivational syndrome in frequent users. This syndrome is seen predominantly in heavy daily users and is characterized by the emergence of decreased drive and ambition. It is also associated with other socially and occupationally impairing symptoms, including a shortened attention span, poor judgment, easy distractibility, impaired communication skills, introversion, and diminished effectiveness in interpersonal situations. Personal habits may deteriorate, and there may be a loss of insight and even feelings of depersonalization. In terms of chronic administration to humans, tolerance to cannabinoids has been well documented, but the question of cannabinoid dependence has always been controversial. The discovery of the brain cannabinoid antagonist SR141716A (Fig. 13 — 16) has settled this question in experimental animals because it precipitates a withdrawal syndrome in mice chronically exposed to THC. It is therefore highly likely, but not yet proved, that dependence also occurs in humans and is presumably due to the same types of adaptive changes in cannabinoid receptors that occur in other neurotransmitter receptors after chronic administration of other drugs of abuse.

Nicotine

Cigarette smoking is a nicotine delivery system. Unfortunately, it also delivers carcinogens and other toxins that damage the heart, lungs, and other tissues as well. In terms of psychopharmacology, nicotine acts directly on nicotinic cholinergic receptors (Fig. 13 — 17) (see discussion of cholinergic neurons in Chapter 12 and Fig.
12 — 10). The reinforcing actions of nicotine are very similar to those of cocaine and amphetamine, since dopaminergic cells in the mesolimbic dopamine pathway receive direct nicotinic cholinergic input, which is stimulated by cigarette smoking (Figs. 13 — 2 and 13 — 18). This mediates the reward experienced by smokers, including elevation of mood, enhancement of cognition, and decrease of appetite. The psychopharmacological and behavioral actions of nicotine, however, appear to be much more subtle than those of cocaine. Whereas cocaine blocks the dopamine transporter and causes a flood of dopamine to act at the dopamine synapse, nicotine may shut down the nicotinic receptor shortly after binding to it (Fig. 13 — 19), so that neither it nor

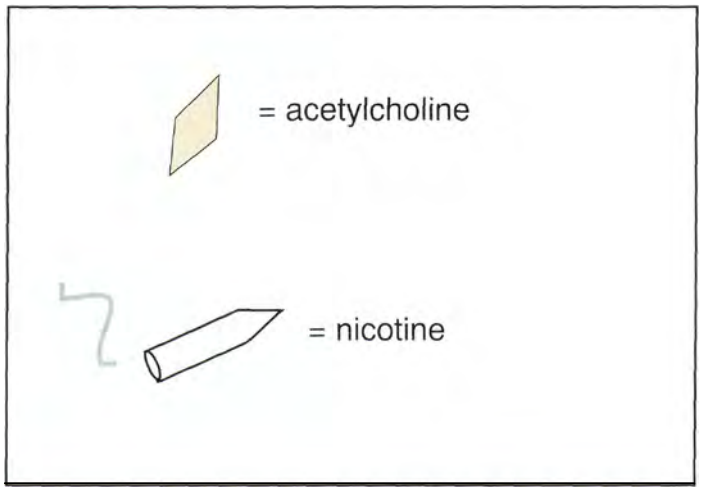


FIGURE 13-17. Icons for **nicotine** and **acetylcholine**.

acetylcholine itself can stimulate the nicotinic receptor any further for a while. Thus, dopaminergic stimulation of mesolimbic dopamine receptors stops after a short period and a small amount of nicotinic stimulation. Instead of the longer and much more intense euphoria of cocaine, the pleasure of nicotine is a desirable but small boost in the sensation of pleasure ("minirush"), followed by a slow decline until the nicotinic receptors switch back on and the smoker takes the next puff or smokes the next cigarette. Nicotine's psychopharmacological effects, therefore, may be somewhat self-regulating, which may explain why its effects on behavior are more limited than the effects of cocaine or amphetamine.

Both stimulant users and smokers may down-regulate their dopamine receptors because of excessive dopamine stimulation. However, nicotine users may up-regulate their nicotinic cholinergic receptors to help compensate for the fact that nicotine keeps turning them off (Fig. 13 — 20). These possible changes in dopamine and nicotine receptors may be related to the psychopharmacological mechanisms underlying nicotine's profound ability to produce dependence and withdrawal.

Dependence on nicotine causes a withdrawal syndrome characterized by craving and agitation, reminiscent of but less severe than that experienced by a stimulant abuser in withdrawal (Fig. 13 — 21). The recent availability of a nicotine delivery system through a transdermal patch is popular as a means to assist patients to detoxify from smoking. The pulsatile delivery of nicotine through smoking (Fig. 13 — 22) can be replaced by continuous delivery through a transdermal skin patch acting similarly to a constant intravenous infusion (Fig. 13 — 23). The idea is that the nicotine and dopamine receptors are allowed to readapt more gradually toward normal than they would if the smoker suddenly became abstinent. The hope is that the withdrawal syndrome is prevented or blunted when nicotine is delivered transdermally. In addition, the nicotine dose can be progressively decreased, depending on how much dose reduction the abstinent smoker can tolerate. The dose is decreased in a slow, stepwise fashion until the patient is able to tolerate complete abstinence from smoking and complete discontinuation of transdermal nicotine delivery. The success of this approach depends on the motivation of the smoker to quit and the

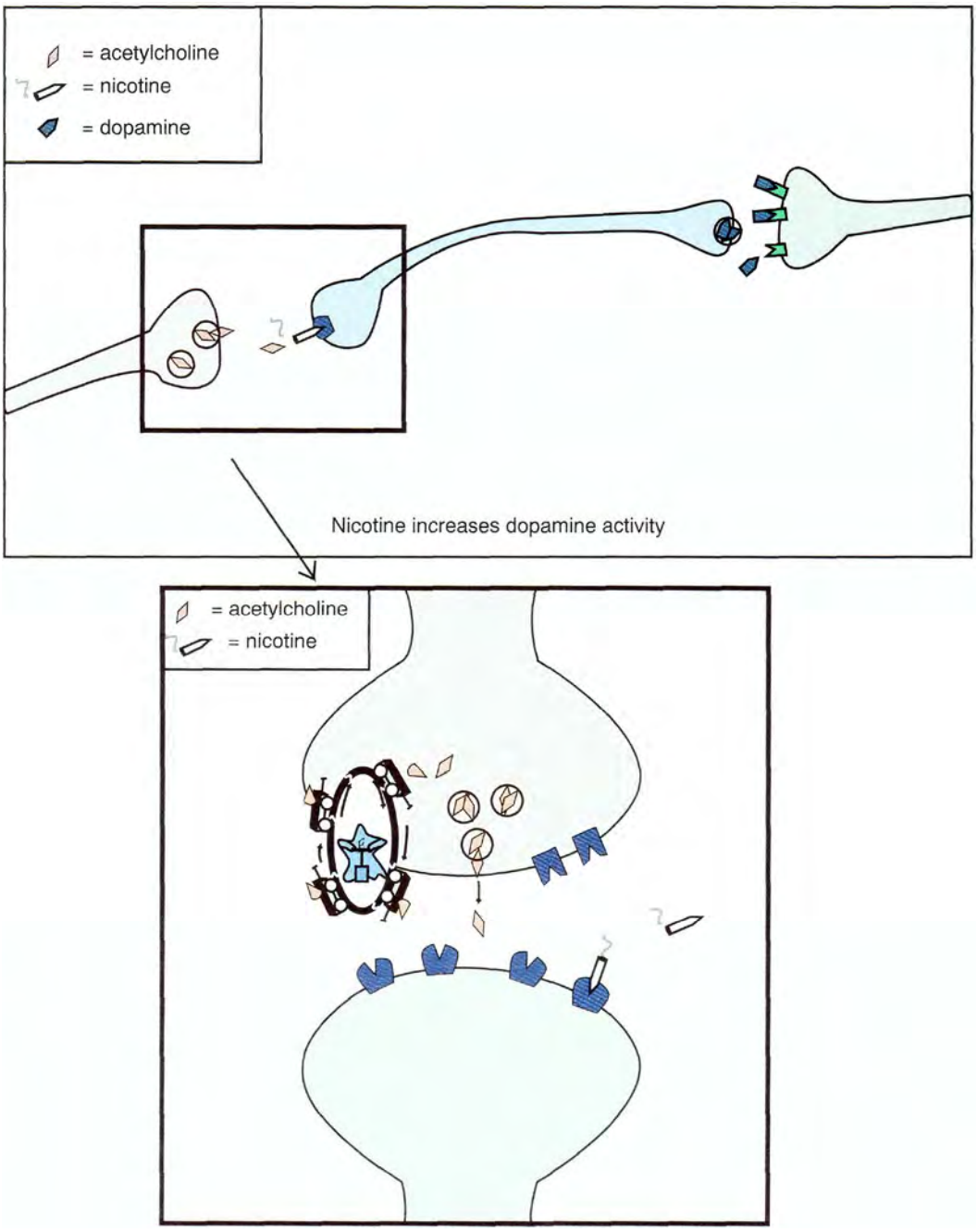


FIGURE 13 — 18. *Pharmacology of nicotine (part 1)*. Nicotine acts directly on nicotinic cholinergic receptors, which are themselves located in part on mesolimbic dopamine neurons. When nicotine stimulates these receptors (A and B), it causes release of dopamine from the mesolimbic neurons and thereby conveys a sense of reward and pleasure.

use of adjunctive psychological support and information programs to help the smoker cope better with abstinence.

Another approach to facilitating smoking cessation is to reduce the craving that occurs during abstinence (Fig. 13 — 21) by boosting dopamine with the dopamine and norepinephrine reuptake inhibitor bupropion (see Figs. 6—48 and 6—49). The idea is to give back some of the dopamine downstream to the craving postsynaptic limbic D2 receptors while they are adjusting to the absence of their dopamine "fix" due to the recent withdrawal of nicotine (Fig. 13 — 24).

Opiates

Opiates act on a variety of receptors. The three most important subtypes are the mu, delta, and kappa opiate receptors (Fig. 13—25). The brain makes its own endogenous opiate-like substances, sometimes referred to as the "brain's own morphine." They are peptides derived from precursor proteins called pro-opiomelanocortin (POMC), proenkephalin, and prodynorphin. Parts of these precursor proteins are cleaved off to form endorphins or enkephalins, stored in opiate neurons, and presumably released during neurotransmission to mediate endogenous opiate-like actions (Fig. 13—25). However, the precise number and function of endogenous opiates and their receptors and their role in pain relief and other central nervous system (CNS) actions remain largely unknown.

Exogenous opiates in the form of pain relievers, such as codeine or morphine, or drugs of abuse, such as heroin, are also thought to act as agonists at mu, delta, and kappa opiate receptors (Fig. 13 — 26), particularly mu receptors. At and above pain-relieving doses, the opiates induce euphoria, which is their main reinforcing property. Opiates can also induce a very intense but brief euphoria, sometimes called a "rush," followed by a profound sense of tranquility, which may last several hours, followed in turn by drowsiness ("nodding"), mood swings, mental clouding, apathy, and slowed motor movements. In overdose, these same agents act as depressants of respiration and can also induce coma. The acute actions of opiates can be reversed by synthetic opiate antagonists, such as naloxone and naltrexone, which compete as antagonists at opiate receptors.

When given chronically, opiates readily cause both tolerance and dependence. Adaptation of opiate receptors occurs quite readily after chronic opiate administration. The first sign of this is the need of the patient to take a higher and higher dose of opiate in order to relieve pain or to induce the desired euphoria. Eventually, there may be little room between the dose that causes euphoria and that which produces the toxic effects of an overdose. Another sign that dependence has occurred and that opiate receptors have adapted by decreasing their sensitivity to agonist actions is the production of a withdrawal syndrome once the chronically administered opiate wears off. The opiate antagonists such as naloxone can precipitate a withdrawal syndrome in opiate-dependent persons. This withdrawal syndrome is characterized by a feeling of dysphoria, craving for another dose of opiate, irritability, and signs of autonomic hyperactivity, such as tachycardia, tremor, and sweating. Piloerection ("goose bumps") is often associated with opiate withdrawal, especially when the drug is stopped suddenly ("cold turkey"). This is so subjectively horrible that the opiate abuser will often stop at nothing in order to obtain another dose of opiate to relieve symptoms of withdrawal. Thus, what may have begun as a quest for euphoria may

end up as a quest to avoid withdrawal. Clonidine, an alpha 2 adrenergic agonist, can reduce signs of autonomic hyperactivity during withdrawal and aid in the detoxification process.

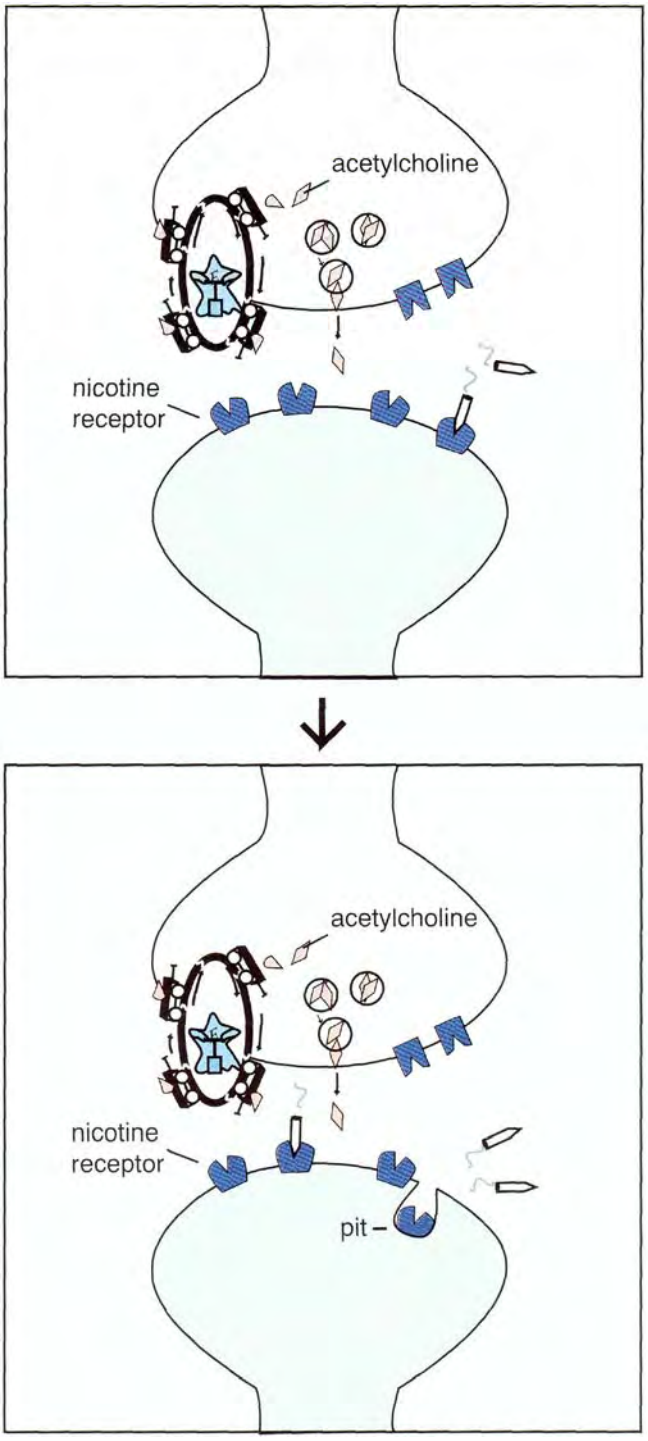
In the early days of opiate use, abuse, and intoxication and prior to completion of the neuroadaptive mechanisms, that mediate opiate receptor desensitization, opiate intoxication alternates with normal functioning. Later, after the opiate receptors adapt and dependency is established, the abuser may experience very little euphoria, but mostly withdrawal-free periods alternating with withdrawal.

Opiate receptors can readapt to normal if given a chance to do so in the absence of additional opiate intake. This may be too difficult for the abuser to tolerate, so reinstitution of another opiate, such as methadone, which can be taken orally and then slowly tapered, may assist in the detoxification process. A partial mu opiate agonist, buprenophine, may also become available in a sublingual dosage formulation to substitute for stronger opiates and then be tapered. It will be combined with the opiate naloxone so that it cannot be abused intravenously. L-Alpha-acetylmethodol acetate (LAAM) is a long-acting orally active opiate with pharmacologic properties similar to those of methadone. Agonist substitution treatments are best used in the setting of a structured maintenance treatment program, which includes random urine drug screening and intensive psychological, medical, and vocational services.

Alcohol

The pharmacology of alcohol is still relatively poorly characterized, and its mechanism of action is nonspecific since alcohol can have effects on a wide variety of neurotransmitter systems. Neither alcohol's acute intoxicating actions nor its chronic effects of dependence, tolerance, and withdrawal are understood very well. However, various research studies do suggest that alcohol acts not only by enhancing inhibitory neurotransmission at GABA-A receptors (Fig. 13 — 27), but also by reducing excitatory neurotransmission at the N-methyl-*d*-aspartate (NMDA) subtype of glutamate receptors (Fig. 13—28). That is, alcohol enhances inhibition and reduces excitation, and this may explain its characterization as a "depressant" of CNS neuronal functioning (Fig. 13 — 29). These effects of alcohol may thus explain some of its in-

FIGURE 13 — 19. *Pharmacology of nicotine (part 2).* Although Figure 13 — 18 suggests that the pharmacology of nicotine shares similarities with the pharmacology of cocaine, the actions of nicotine appear to be much more subtle than those of cocaine. Whereas cocaine blocks the dopamine transporter and causes a flood of dopamine to act at the dopamine synapse, nicotine stimulation of nicotinic receptors (Fig. 13-19A) may shut down the nicotinic receptor by causing it to withdraw into a membrane pit (Fig. 13 — 19B) shortly after binding to it, so that it cannot stimulate the nicotinic receptor any further for a time. Thus, dopaminergic stimulation of mesolimbic dopamine receptors stops after a short time and small amount of nicotinic stimulation. Instead of the longer and much more intense euphoria of cocaine, the pleasure of nicotine is a desirable but small boost in the sensation of pleasure (mini-"rush"), followed by a slow decline until the nicotinic receptors switch back on and the smoker takes the next puff or smokes the next cigarette. Nicotine's psychopharmacological effects, therefore, may be somewhat self-regulating, which may explain why its effects on behavior are more limited than the effects of cocaine or amphetamine.



Nicotine will "turn off"
its own receptor for a time

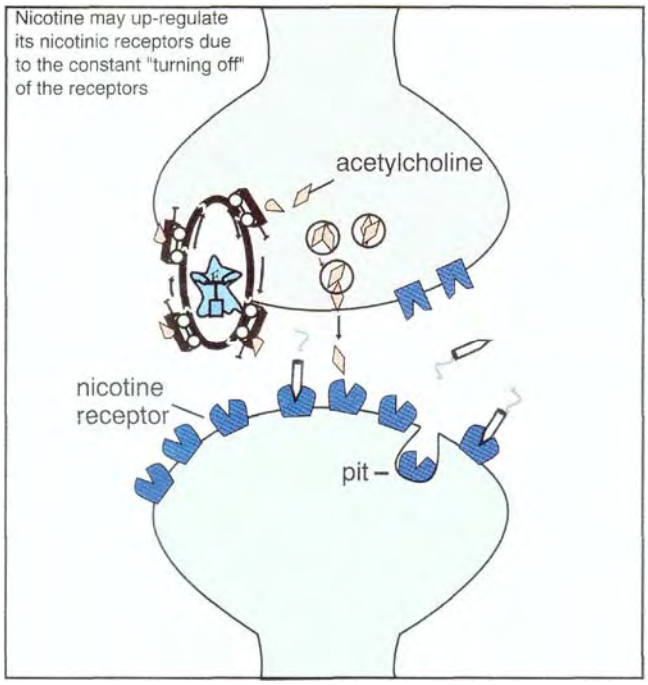


FIGURE 13 — 20. *Pharmacology of nicotine (part 3).* Over time, smokers may eventually up-regulate their nicotinic cholinergic receptors to help compensate for the fact that nicotine keeps turning them off. These changes in nicotine receptors may be related to the psychopharmacological mechanisms underlying nicotine's profound ability to produce dependence and withdrawal.

toxicating, amnestic, and ataxic effects. However, alcohol's reinforcing effects are theoretically mediated by the effects that its changes in GABA and glutamate have on dopamine release in the mesolimbic dopamine system (Fig. 13 — 2). Furthermore, it also seems to release both opiates and cannabinoids in the reward system. Blocking cannabinoid receptors in animals reduces craving for alcohol in alcohol dependent animals. Blocking opiate receptors with naltrexone (Fig. 13 — 29) in alcohol-dependent humans decreases craving and thereby increases abstinence rates. If one drinks when taking naltrexone, the opiates released do not lead to pleasure, so why bother drinking? (Some patients may also say, why bother taking naltrexone, of course, and relapse back into drinking alcohol. Naltrexone is recommended for use in the first 90 days of abstinence, when the risk of relapse is highest; however, it has been shown to be generally safe and well tolerated by alcoholic patients for up to a year. Nalmefene (is a mu opioid antagonist, which is also being tested in alcoholics to determine whether it increases abstinence rates.

Alcamprosate, a derivative of the amino acid taurine, interacts with the NMDA receptor and perhaps can substitute for this effect of alcohol during abstinence (Fig. 13 — 30). Thus, when alcohol is withdrawn and the mesolimbic D2 receptors are whining for dopamine because of too much glutamate, perhaps alcamprosate substitution will reduce the neuronal hyperexcitability of alcohol withdrawal, resulting

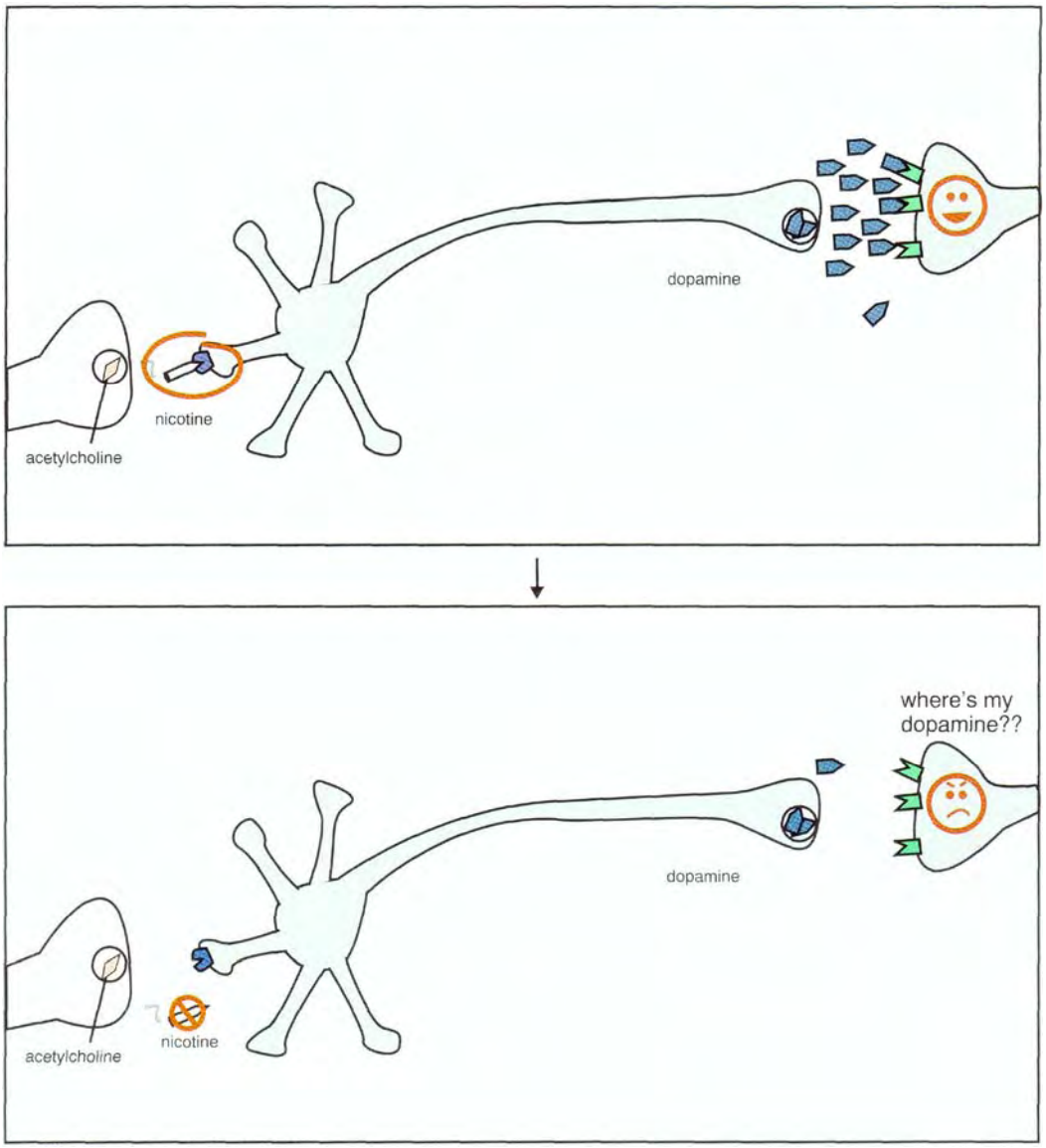


FIGURE 13-21. In the top panel, a regular **smoker delivers reliable nicotine** (red circle), releasing dopamine in the limbic area at frequent intervals, which is very rewarding to the limbic dopamine 2 (D2) receptors on the right. However, during attempts at smoking cessation, dopamine will be cut off when nicotine no longer releases it from the mesolimbic neurons. This upsets the postsynaptic D2 limbic receptors and leads to craving and what some call a **"nicotine fit."**

in reduced withdrawal distress and craving. Alcamprosate is marketed in Europe and is being tested extensively in the United States.

The subject of how to treat alcohol abuse and dependence is complex, and the most effective treatments are still 12-step programs, which are beyond the scope of this text.

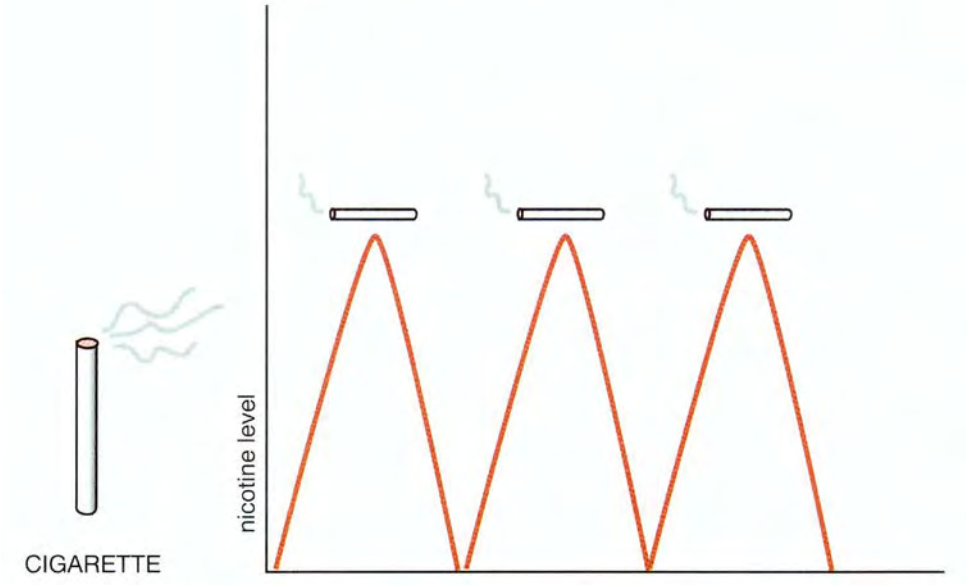


FIGURE 13 — 22. Cigarette smoking is a *pulsatile nicotine delivery system.* Dependence on nicotine causes a withdrawal syndrome between cigarettes as the nicotine level leaves the blood and the brain. If allowed to progress without another cigarette being smoked, withdrawal from nicotine is characterized by craving and agitation, suggestive of a less severe version of a stimulant abuser in withdrawal.

Benzodiazepines and Sedative-Hypnotics

Benzodiazepines

We have already discussed extensively in Chapter 8 the mechanism of the therapeutic actions of benzodiazepines as anxiolytics and sedative-hypnotics and their pharmacologic mechanism as allosteric modulators of GABA-A receptors (Figs. 8 — 19 to 8 — 24). This causes a net boosting of chloride conductance through a chloride channel, enhancing inhibitory neurotransmission and causing anxiolytic actions (Fig. 13 — 31). Such actions are also thought to underlie the production of the reinforcing properties of euphoria and a sedating sort of tranquility, which causes some individuals to abuse these drugs (Fig. 13 — 2). Excessive actions of benzodiazepines at the same receptors that mediate their therapeutic actions are thought to be the psycho-pharmacological mechanism of euphoria, drug reinforcement, and at an extreme, overdose.

When benzodiazepines are used or abused chronically, they may cause adaptive changes in benzodiazepine receptors such that their power to modulate GABA-A receptors in response to a benzodiazepine decreases with time (Fig. 13 — 32). These patients may become irritable or anxious or even experience panic attacks if they suddenly stop taking the drugs (Fig. 13 — 33). This shift in benzodiazepine abusers to a desensitized receptor (Fig. 13 — 32) may manifest itself as the need to take higher doses of benzodiazepines to get "high." This receptor desensitization is most likely to be uncovered once chronic abusive benzodiazepine administration is discontinued, particularly if discontinuation is sudden (Fig. 13 — 33). This desensitized receptor worsens the impact of benzodiazepine discontinuation because the brain, which is

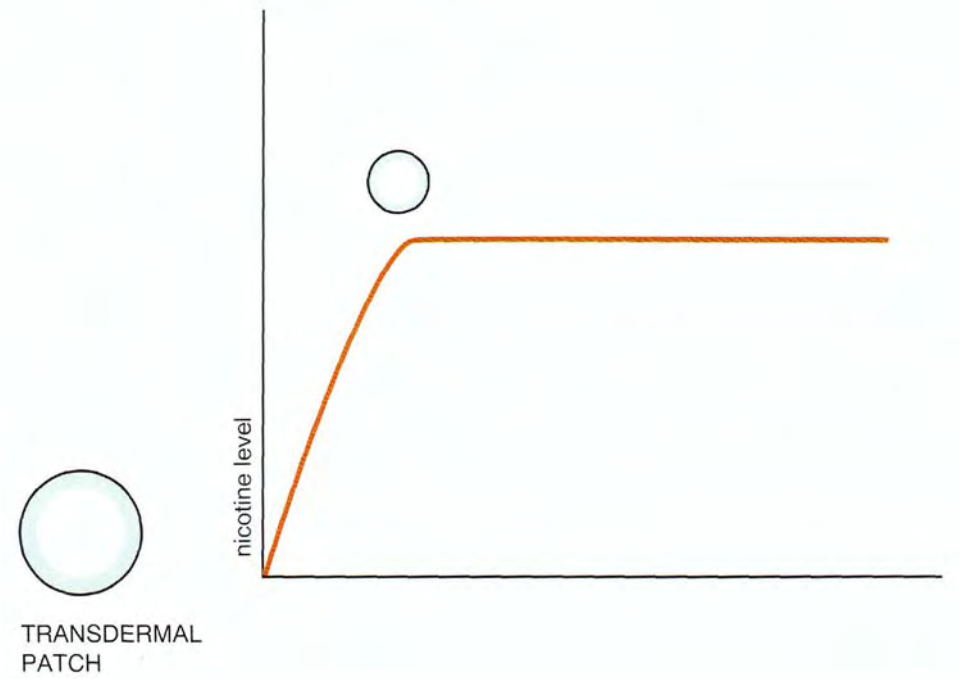


FIGURE 13 — 23. *Transdermal nicotine administration for the treatment of nicotine withdrawal.* A recently available nicotine delivery system through a transdermal patch is popular as an adjunct in assisting patients to detoxify from smoking. The pulsatile delivery of nicotine through smoking (Fig. 13 — 22) can be replaced by continuous delivery through a transdermal skin patch, acting similarly to a constant intravenous infusion. The idea is that the nicotine and dopamine receptors are allowed by readapt more gradually to normal than would happen if the smoker suddenly became abstinent. The hope is that the withdrawal syndrome is prevented or blunted when nicotine is delivered transdermally. In addition, the nicotine dose can be progressively decreased depending on how much nicotine dose reduction the abstinent smoker can tolerate. The amount of reduction is increased in a slow, stepwise fashion until the patient is able to tolerate complete abstinence from smoking and complete discontinuation of transdermal nicotine delivery. The success of this approach depends on the motivation of the smoker to quit and the use of adjunctive psychological support and information programs to help the smoker cope better with abstinence.

used to too much benzodiazepine at its receptors, is suddenly starved for benzodiazepine. Therefore, the brain experiences the reverse of benzodiazepine intoxication, namely, dysphoria and depression instead of euphoria, anxiety and agitation instead of tranquility and lack of anxiety, insomnia instead of sedation and sleep, muscle tension instead of muscle relaxation, and at worst, seizures instead of anticonvulsant effects. These actions continue either until benzodiazepine is replaced or until the receptors readapt to the sensitivity they had prior to excessive use of the benzodiazepines. Alternatively, one can reinstitute benzodiazepines but taper them slowly, so that the receptors have time to readapt during dosage reduction and withdrawal symptoms are prevented.

Sedative-Hypnotics

The pharmacologic mechanisms of drugs are basically the same as those described above for the benzodiazepines. However, these drugs are much less safe in overdose,

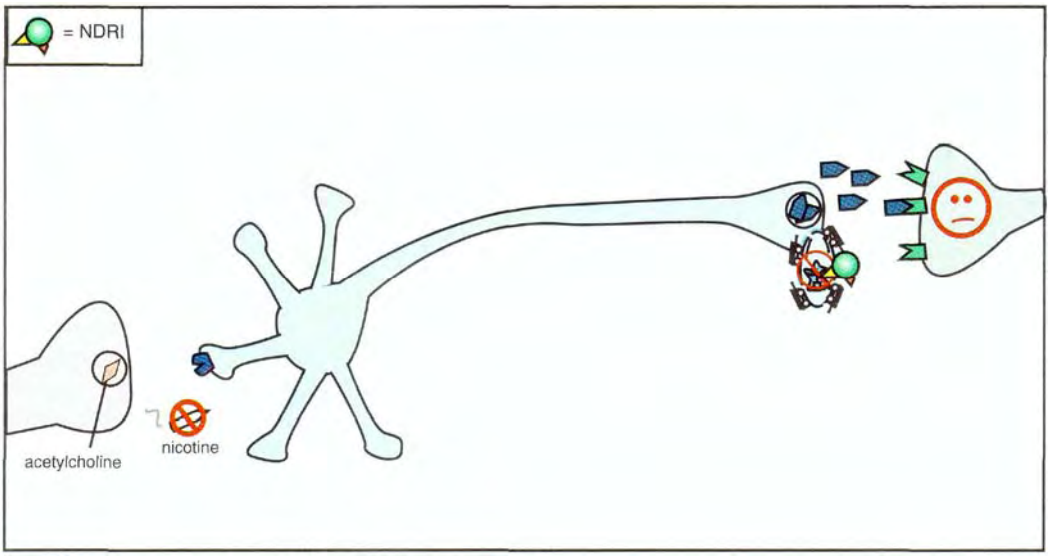


FIGURE 13 — 24. Rather than substitute a nicotine patch for nicotine cigarettes in **smoking cessation,** another therapeutic approach to diminishing craving during the early stages of smoking cessation is to **deliver a bit** of **dopamine** itself by blocking dopamine reuptake directly at the nerve terminal with bupropion. Although not as powerful as nicotine, it does take the edge off and makes abstinence more tolerable.

cause dependence more frequently, are abused more frequently, and produce much more dangerous withdrawal reactions. Apparently, the receptor mediating the pharmacologic actions of these agents, presumably an allosteric modulator at GABA-A ligand-gated chloride channels, is even more readily desensitized with even more dangerous consequences than the benzodiazepine receptor (Fig. 13 — 34). It must also mediate a more intense euphoria and a more desirable sense of tranquility than the benzodiazepine receptor. Since benzodiazepines are frequently an adequate alternative therapy for these drugs, physicians can help minimize abuse of these agents by prescribing them rarely if ever. In the case of withdrawal reactions, reinstituting and then tapering the offending agent under close clinical supervision can assist the detoxification process. These agents include barbiturates and related compounds such as ethclorvynol and ethinamate, chloral hydrate and derivatives; and piperidinedione derivatives such as glutethimide and methyprylon.

Psychopharmacology of Obesity: My Receptors Made Me Eat It

Metabolism and energy utilization are peripheral endocrine actions. Recent discoveries are lending important insights into how these central and peripheral components of weight control are mediated by receptors for several key neurotransmitters and hormones. Since obesity results from an imbalance between caloric intake and energy expenditure, these new findings suggest that treatment of obesity in the future perhaps will be based both on central mechanisms, which decrease the urge to eat, and on peripheral mechanisms, which increase the mobilization of energy. At present, however, it is useful to be aware that chronic treatment with many psy-

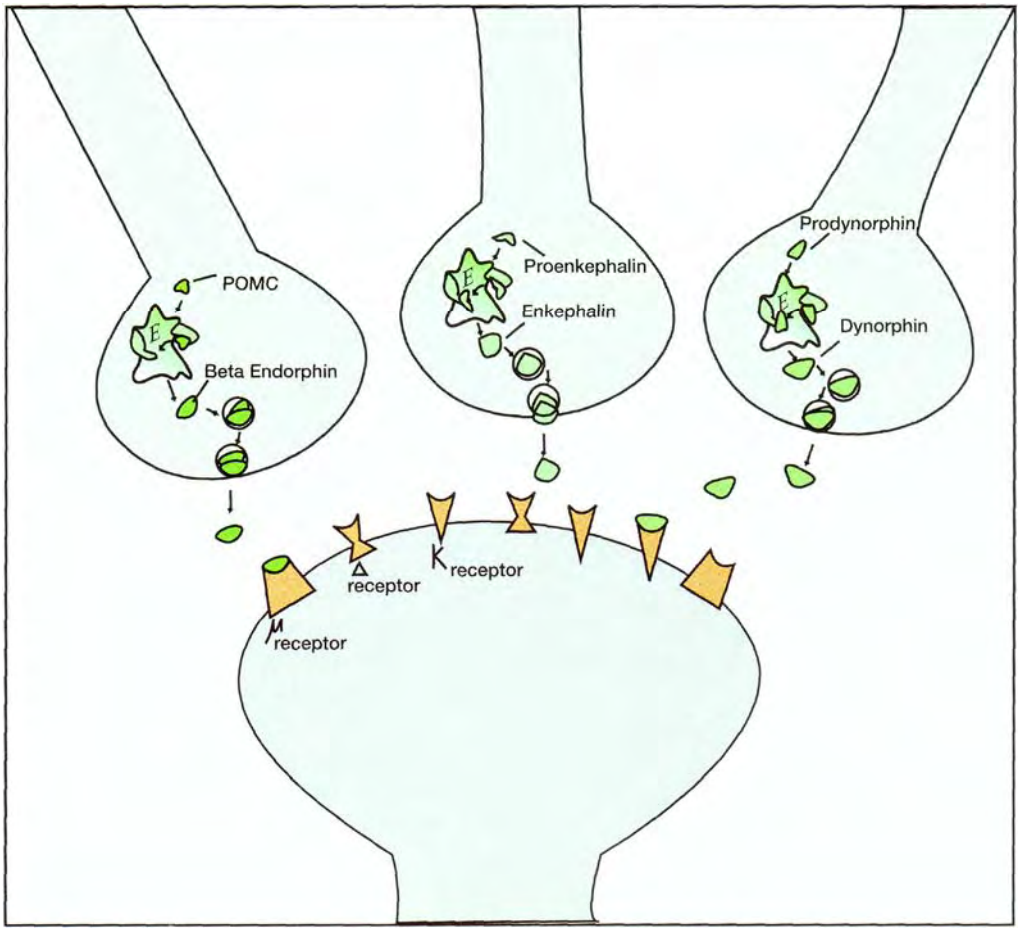


FIGURE 13 — 25. *Pharmacology of the endogenous opiate systems.* The brain makes its own endogenous opiate-like substances, sometimes referred to as the "brain's own morphine-like molecules." They are peptides derived from a precursor proteins called pro-opiomelanocortin (POMC), proenkephalin, and prodynorphin. Parts of these precursor proteins are cleaved off to form endorphins or enkephalins, stored in opiate neurons, and presumably released during neurotransmission to mediate endogenous opiate-like actions. However, the precise number and function of endogenous opiates and their receptors and their role in pain relief and in other CNS actions remain largely unknown.

chotropic drugs can be associated with changes in weight, particularly weight gain. This is increasingly recognized as a problem for atypical antipsychotics (Table 13 — 2), although it can also be a problem for many other classes of psychotropic drugs, including antidepressants. Some individuals may abuse stimulants and nicotine for their ability to control weight gain or may struggle with weight gain problems when they try to become abstinent from these agents. Therefore, a brief discussion of the role of receptors and weight is included in this chapter.

Histamine-1 Receptors

The exact neurotransmitter role of histamine in the CNS remains an enigma. However, regulation of arousal and appetite by histamine has long been suggested by

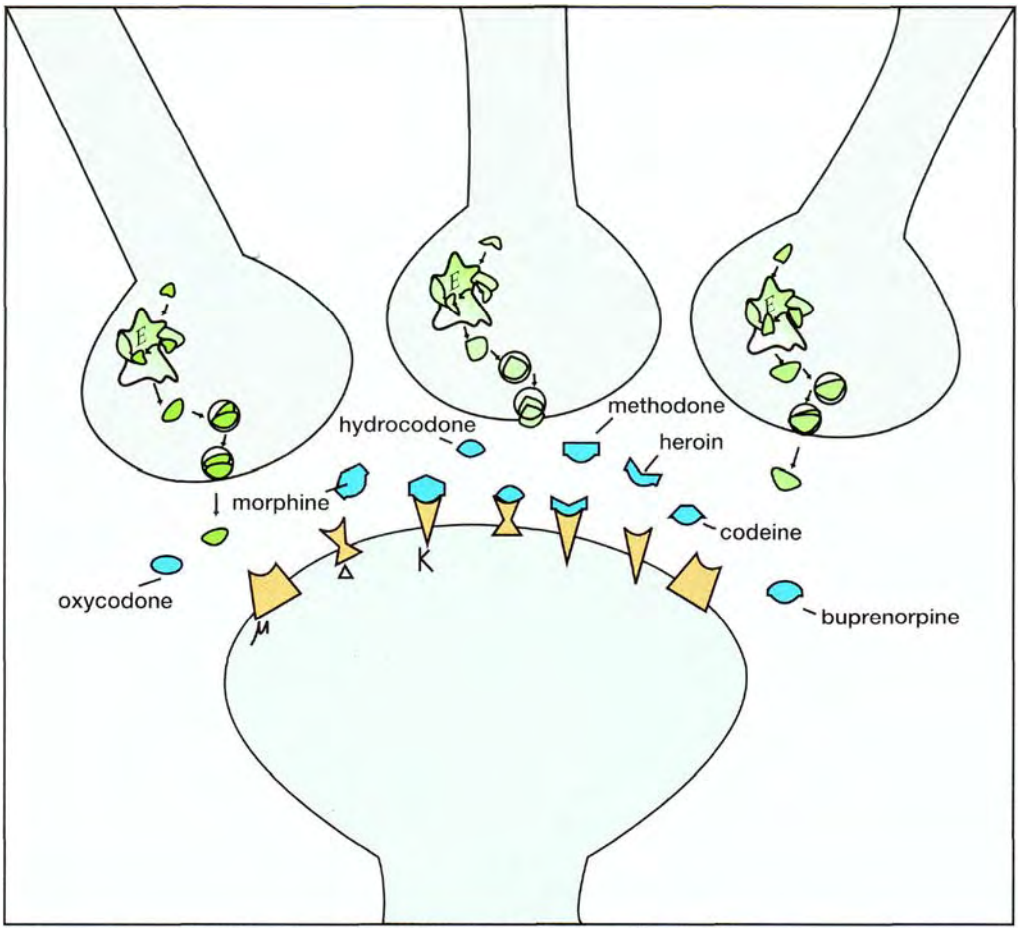


FIGURE 13-26. *Pharmacological actions of opiate drugs.* Opiate drugs act on a variety of receptors, called opiate receptors. Acute actions of opiate drugs cause relief of pain by acting as agonists at opiate receptor subtypes. At and above pain-relieving doses, the opiate drugs induce euphoria, which is the main reinforcing property of the opiates. In sufficient doses, opiates induce a very intense but brief euphoria sometimes called a "rush," followed by a profound sense of tranquility, which may last several hours and is followed in turn by drowsiness ("nodding"), mood swings, mental clouding, apathy, and slowed motor movements. In overdose, these same agents act as depressants of respiration and can also induce coma.

observations that histamine-1 antagonists not only are sedating but also increase appetite and weight in experimental animals and humans. Binding studies of antidepressants and antipsychotics suggest that sedation and weight gain in humans art-proportional to their ability to block these histamine receptors. In fact, binding to these receptors correlates best with weight gain among the actions of psychotropic drugs.

5-HT2C Receptors

For many years, pharmacologists have known that increasing the availability of serotonin (5-HT) in the synaptic cleft or direct activation of 5-HT receptors reduces

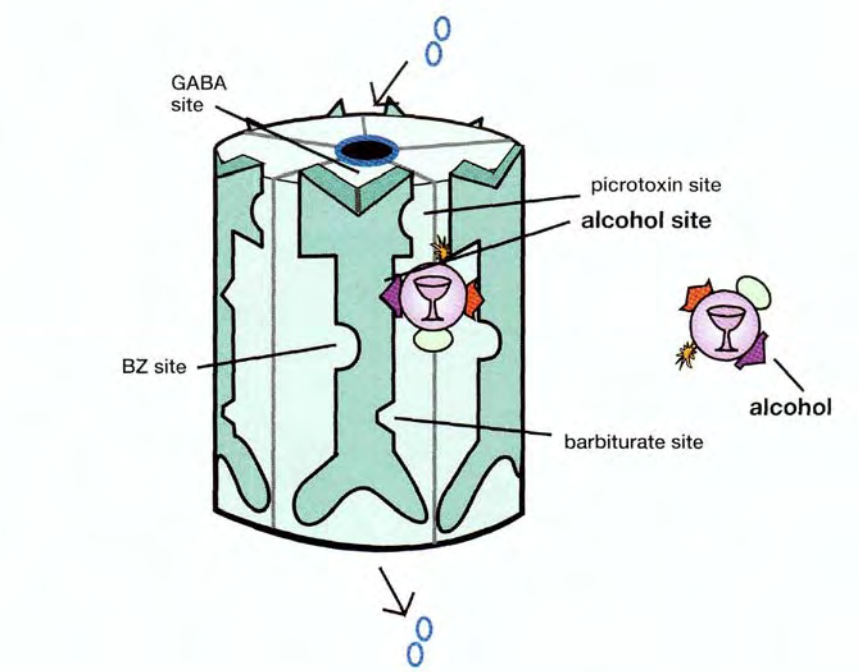


FIGURE 13 — 27. **Alcohol** mediates some of its pharmacologic effects by enhancing the actions of the **inhibitory GABA A** receptor complex—that is, it enhances inhibition.

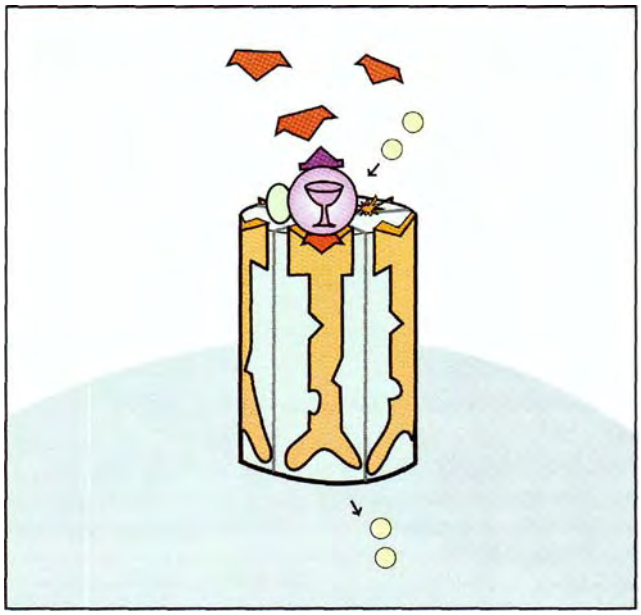


FIGURE 13 — 28. **Alcohol** mediates some of its pharmacologic effects by decreasing the actions of the **excitatory NMDA** receptor complex—that is, it diminishes excitation.

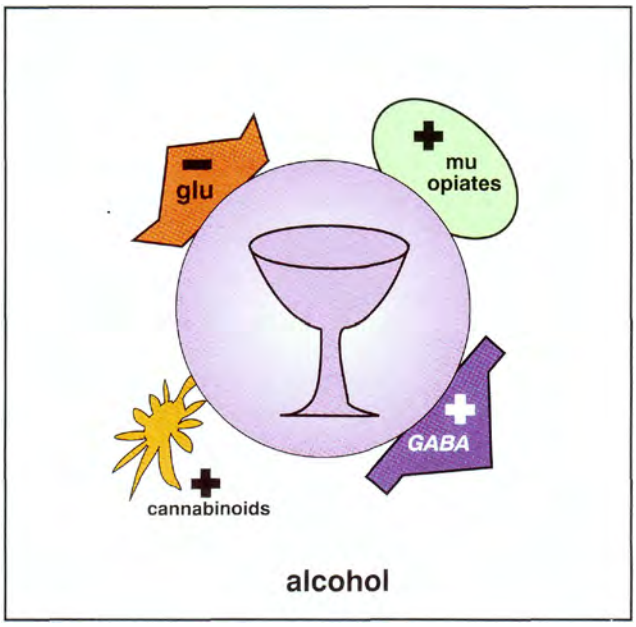


FIGURE 13 — 29. Icon of **alcohol**. In addition to enhancing GABA inhibition and reducing glutamate excitation, alcohol also enhances euphoric effects by releasing opiates and endocannabinoids, perhaps thereby mediating its "high."

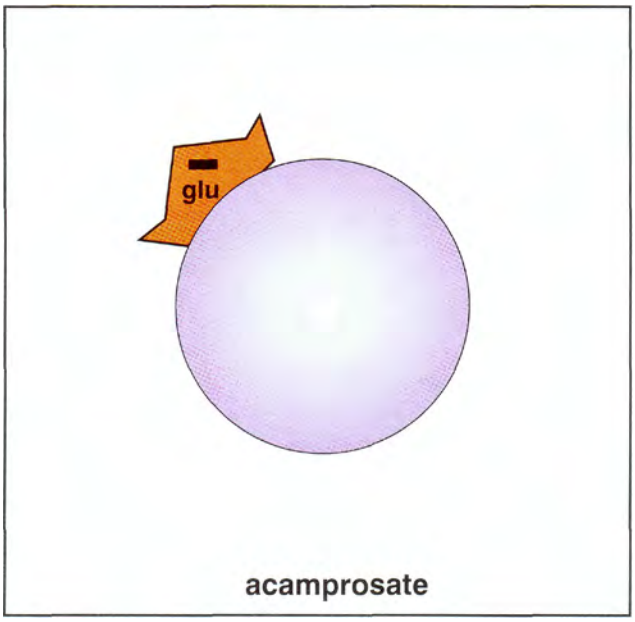


FIGURE 13 — 30. Icon of **acamprosate**. A structural analogue of the amino acid taurine, acamprosate reduces the excitatory actions of glutamate at the NMDA—calcium channel complex.

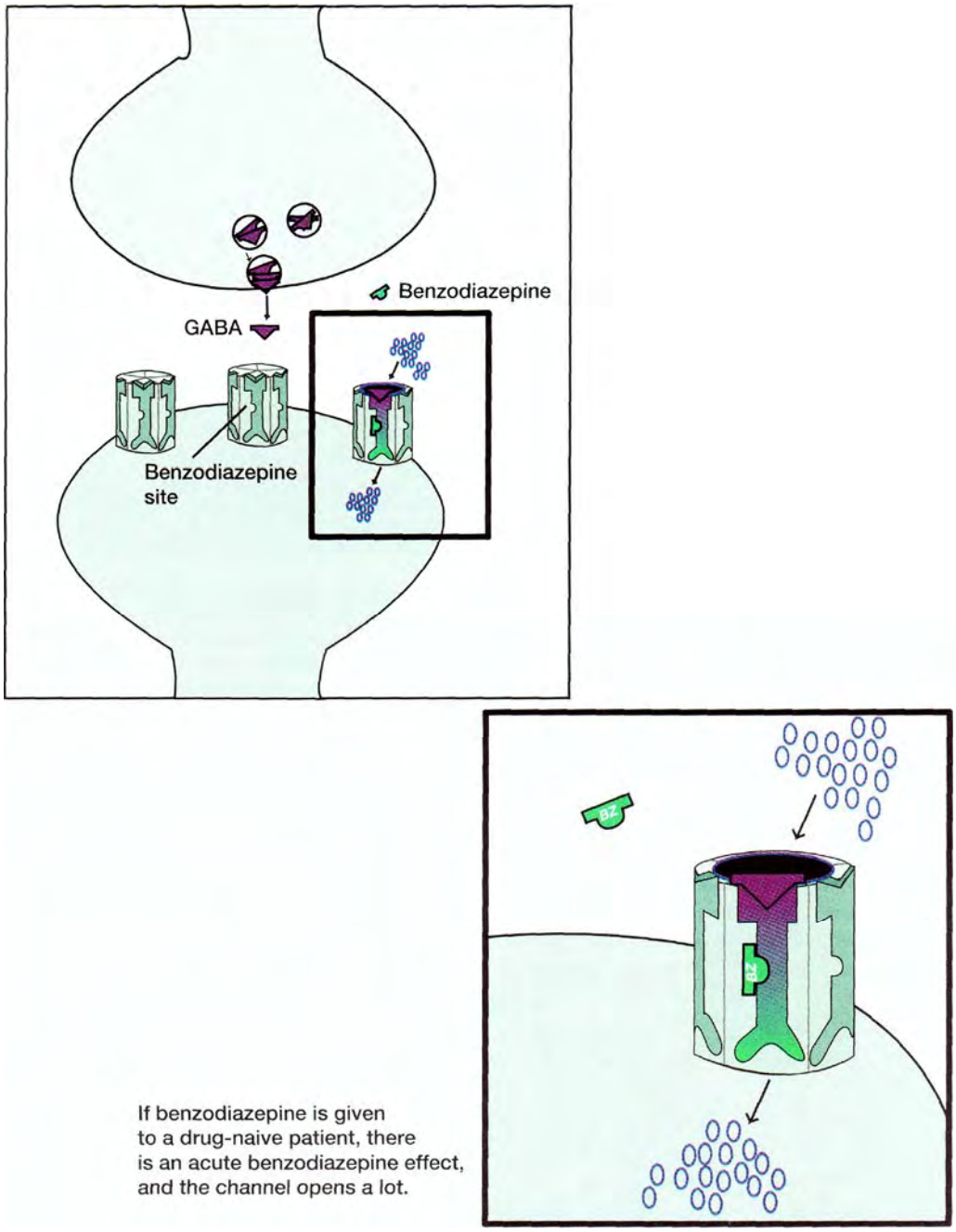


FIGURE 13 — 31. *Acute administration of a benzodiazepine to a nondependent individual.* Benzodiazepines act as allosteric modulators of GABA-A receptors. If a benzodiazepine is given to a drug-naive patient, there is an acute benzodiazepine effect, opening the chloride channel maximally. This causes a net boosting of chloride conductance through a chloride channel, enhancing inhibitory neurotransmission and causing anxiolytic actions. Such actions are also thought to underlie production of the reinforcing properties of euphoria or a sedating sort of tranquility, which causes some individuals to abuse these cirugs. Excessive actions of benzodiazepines at the same receptors that mediate their therapeutic actions is thought to be the psychopharmacological mechanism of euphoria, drug reinforcement, and at an extreme, overdose.

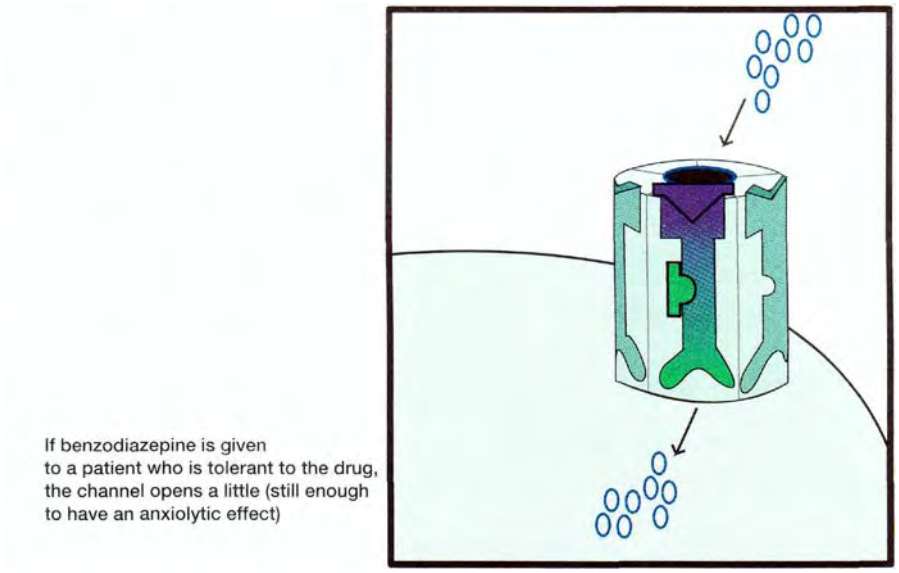


FIGURE 13 — 32. *Chronic administration of a benzodiazepine to an individual who has developed tolerance and dependence.* When benzodiazepines are used or abused chronically, they may cause *adaptive changes* in benzodiazepine receptors, such that they become increasingly less powerful in modulating GABA-A receptors in response to a benzodiazepine. Administration of a benzodiazepine to such an individual causes the chloride channel to open less than before but still enough to give an anxiolytic or perhaps a euphoric and drug-reinforcing effect. That effect may be diminished, however, in comparison with acute administration prior to the development of this desensitization and tolerance.

food consumption, while decreasing 5-HT receptor activation brings about the opposite effect. Recent research more specifically implicates the 5-HT2C receptor subtype as playing the key role in regulating appetite. For example, mutant mice that lack the 5-HT2C receptor are obese. Activating 5-HT2C receptors decreases eating behavior in rats. A 5-HT2C mechanism may also underlie weight reduction in humans taking appetite suppressants. Serotonin selective reuptake inhibitors (SSRIs) can also reduce appetite, at least acutely. Fluoxetine, arguably the most anorexigenic of the SSRIs and with a specific indication for bulimia, is also the only SSRI with direct 5-HT2C agonist activity in addition to its 5-HT reuptake blocking properties (see Chapter 6 and Fig. 6—41). The most recently marketed appetite suppressant is sibutramine. Its mechanism works by both 5-HT and norepinephrine reuptake blockade, much like higher doses of venlafaxine (see Chapter 7 and Figs. 7 — 1 and 7 — 2). Drugs that block 5HT2C receptors as well as histamine-1 receptors are especially associated with weight gain, although blocking 5HT2C receptors alone is not necessarily associated with weight gain (see Chapter 11 and Table 13 — 2).

Beta3-Adrenergic Receptors

The three distinct subtypes of beta receptors are the beta1-adrenergic receptor, which is predominantly a cardiac receptor and the target of beta-blockers; the beta2-

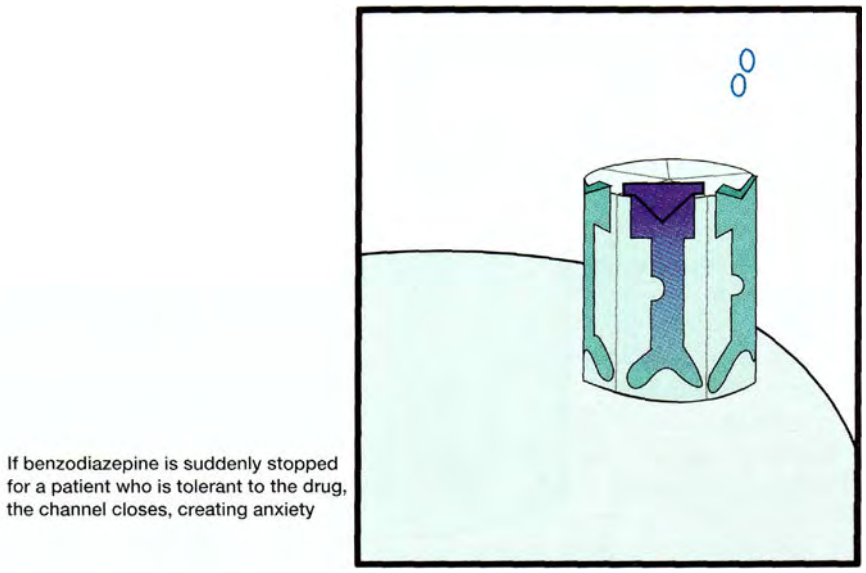


FIGURE 13 — 33. *Acute withdrawal of benzodiazepines in a benzodiazepine-dependent individual.* If benzodiazepines are suddenly stopped in a patient who is tolerant to them and dependent on them, benzodiazepine receptors will experience this as an *acute deficiency* at their binding sites. Thus, the presence of desensitized benzodiazepine receptors actually worsens the impact of benzodiazepine discontinuation. The brain, which is used to too much benzodiazepine at its receptors, is suddenly starved for benzodiazepine. Therefore, the brain experiences the reverse of benzodiazepine intoxication, namely, dys-phoria and depression instead of euphoria; anxiety and agitation instead of tranquility and lack of anxiety; insomnia instead of sedation and sleep; muscle tension instead of muscle relaxation; and at worst, seizures instead of anticonvulsant effects. These actions continue either until benzodiazepine is replaced or until the receptors readapt to the sensitivity they had prior to excessive benzodiazepine use. Alternatively, one can reinstitute benzodiazepines but taper them slowly, so that the receptors have time to readapt during dosage reduction, and withdrawal symptoms are prevented.

adrenergic receptor, which is in the lungs, where it is the target of bronchodilating agonists, and is also found in the uterus and skeletal muscle; and the beta3-adrenergic receptor, expressed primarily in adipose tissue, where it regulates energy metabolism and thermogenesis (from fat) especially in response to norepinephrine.

Evidence that the beta3-adrenergic receptors play an active role in weight control in humans comes from the finding that a genetic variant of this receptor constitutes a susceptibility factor for the onset of morbid obesity as well as non-insulin-dependent diabetes. Specifically, this variant of the beta3-adrenergic receptor is associated with hereditary obesity in Pima Native Americans from Arizona and has been demonstrated to have an increased incidence in obese patients in Japan. It also exists in nonobese individuals, including one-fourth of African-Americans and about 10% of the general population in Europe and the United States. The various findings suggest a strategy for treating obesity by stimulating metabolism and peripheral burning of fat rather than by acting on central satiety. Sibutramine, for example, increases norepinephrine peripherally at the beta3-adrenergic receptors in adipose tissue, thereby stimulating thermogenesis, increasing oxygen consumption, and thus leading to weight loss.

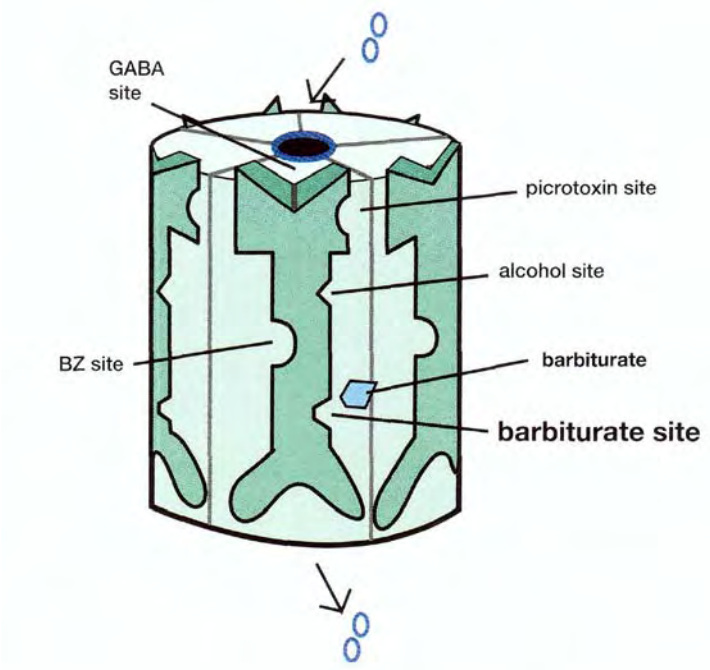


FIGURE 13 — 34. *Pharmacology of sedative-hypnotic-depressant abuse.* The pharmacologic mechanism of action of these drugs is not yet proven but is thought to be basically the same as that described for the benzodiazepines, namely allosteric modulators at GABA-A ligand-gated chloride channels.

Table 13 — 2. *Weight gain and antipsychotics {drugs listed in order of increasing weight gain likelihood)*

Loxapine (no weight gain or weight loss)
Molindone
Ziprasidone
Thiothixene
Haloperidol
Risperidone
Chlorpromazine
Sertindole
Quetiapine
Thioridazine
Olanzapine
Zotepine
Clozapine (the most weight gain)

Neuropeptide Receptors and the Leptin Story

At least three peptides are implicated in the regulation of food intake, energy expenditure, and whole-body energy balance in both rodents and humans and are found both peripherally as hormones and centrally. These are galanin, neuropeptide Y, and

leptin. The physiologic roles of these peptides in regulating body weight via their CNS receptors remain somewhat obscure, although the effects of leptin on food intake and energy expenditure are thought to be mediated centrally via neuropeptide Y.

The role of peripheral leptin has been more extensively investigated. Leptin, a member of the interleukin 6 cytokine family, is a peptide found in multiple tissues and secreted by white adipose cells, where it is highly correlated with body fat mass and size of fat cells. The peripheral effects of leptin include regulation of insulin secretion and energy metabolism in fat cells and skeletal muscle, where it seems to play a role in ensuring the maintenance of adequate energy stores, and thereby protects against starvation. It also acts as a metabolic signal that regulates the effect of nutritional status on reproductive function. Cortisol and insulin are potent stimulators of leptin, whereas beta-adrenergic agonists reduce leptin expression.

Administration of leptin to genetically obese mice reduces their food intake and makes them lose weight. Congenital leptin deficiency in humans is associated with severe early-onset obesity. Somewhat paradoxically, however, plasma leptin levels are increased in obese women and decreased in women with anorexia nervosa. Plasma neuropeptide Y and galanin levels are also increased in obese women. Since leptin levels are chronically increased in obese humans, this suggests that obesity may be associated with malfunctioning leptin receptors, a condition called *leptin resistance*, since leptin is unable to generate an adequate response when its receptor is occupied. Improving responsiveness to leptin may be one key to weight loss.

Understanding the neuropharmacology of weight gain will hopefully lead to better management of obesity. In the meantime, prescribers of psychotropic drugs should monitor weight and body mass index and attempt to select drugs that prevent obesity, as well as to manage obesity when it occurs.

Summary

In this chapter we have attempted to emphasize the psychopharmacological mechanisms of the actions of drugs of abuse and have used these mechanisms to describe drug dependence as well. We have attempted to define the terms frequently used in describing drug abuse and dependence, including abuse, addiction, dependence, reinforcement, tolerance, cross-tolerance and cross-dependence, withdrawal, relapse, and rebound.

We have described the mesolimbic dopamine pathway and the neuropharmacology of reward and have specifically emphasized the mechanism of action of several classes of drugs of abuse, including stimulants (cocaine and amphetamines), hallucinogens, designer drugs and phencyclidine, nicotine, marijuana, opiates, alcohol, benzodiazepines, and sedative-hypnotics. We have even mentioned how receptors and the mesolimbic dopamine pathway could play a role in the psychopharmacology of obesity.