3

Tolerance, Withdrawal, Sensitization, and Conditioning of Drug Effects

TOLERANCE

In the year 63 B.C., Mithradates VI, king of Pontus, tried to commit suicide by poisoning himself. Mithradates was a great leader and a great warrior; he had defeated the Roman legions and spread his influence over Asia Minor. But in 63 B.C., he had been defeated by the Roman general Pompey, and his son had just led a successful revolt against him. To end it all, the king took a large dose of poison, but it had no effect on him. He was finally forced to have one of his Gallic mercenaries dispatch him.

What was the source of the king's resistance to poison? King Mithradates was also a good pharmacologist. Throughout his life, he lived in great fear of being poisoned, so, to protect himself, he repeatedly took increasing doses of poison until he could tolerate large amounts without ill effects. This effect has been called *mithradatism* (Lankester, 1889) after the king; today, we know it as *tolerance*. Mithradatism was also practiced by other historical figures, including Vespasia, the mother of the Roman emperor Nero, and the infamous Lucretia Borgia.

Drug tolerance is defined either as the decreased effectiveness (or potency) of a drug that results from repeated administrations or as the necessity of increasing the dose of a drug in order to maintain its effectiveness after repeated administrations. The term *tolerance* is frequently used in a way that suggests that all the effects of a drug diminish at the same rate, but this is usually not the case. Some effects of a drug may develop tolerance very quickly, some other effects may only show tolerance slowly, and some effects may never show tolerance, no matter how often the drug is given. Among the effects of morphine, for example, are nausea and vomiting. These effects show rapid tolerance, but the ability of morphine to constrict the pupils of the eyes shows no tolerance at all, no matter how long the drug is taken. Because tolerance to different effects of a drug develops at different rates, it is apparent that many mechanisms must be responsible for tolerance (Young & Goudie, 1995). For this reason, it is more appropriate to think of tolerance developing to the effect of a drug rather than to the drug itself (J. Stewart & Badiani, 1993).

When tolerance develops, it does not last indefinitely. Tolerance may disappear with the passage of time, after the use of a drug has been discontinued.

As with the development of tolerance, the disappearance of different drug effects may take place at different rates and may depend on the circumstances in which it is administered.

Tolerance to one drug may well diminish the effect of another drug. This phenomenon, called *cross-tolerance*, is usually seen between members of the same class of drugs. All opiate drugs, for example, will show cross-tolerance. Cross-tolerance is sometimes taken as evidence that the drugs may be producing their effect by common mechanisms.

It is usually assumed that a drug must be given repeatedly before tolerance can occur, but some effects of some drugs may show tolerance after only one or two administrations. This type of tolerance is known as *tachyphylaxis*. It is also possible to demonstrate that tolerance may develop during a single administration of a drug. As we have seen in Chapter 1, after a drug is taken into the body, the level of the drug in the blood rises and then falls. With some drugs, it has been shown that their effect is greater at a specific blood level soon after administration, when the level is rising, than at that same point later, when the level of the drug is falling. This indication that tolerance developed during a single administration is called *acute tolerance*. A good example of acute tolerance is given in Chapter 6.

MECHANISMS OF TOLERANCE

Metabolic Tolerance

Metabolic tolerance (also called *dispositional tolerance*) arises from an increase in the rate at which the body is able to metabolize and get rid of a drug. For the most part, this is a result of enzyme induction, an increase in the level of the enzyme the body uses to destroy the drug (see Chapter 1). When a drug is given repeatedly, it may induce or increase the action of the enzyme the body uses to destroy it. With increases in the rate of metabolism, a given amount of a drug will not reach the same peak levels and will not last as long, so that more and more of the drug will be needed to produce the same effect. When metabolic tolerance takes place, all effects of the drug will be diminished because of the diminished concentration of the drug at the site of action.

Exemplos? (alcohol)

Physiological Tolerance

Physiological tolerance is also known as *cellular* or *pharmacodynamic* tolerance. These terms generally describe a type of tolerance that arises from adjustments made by the body to compensate for an effect of the continued presence of a drug. It is generally believed that such adjustments are a result of a process called *homeostasis*. Many of the body's physiological processes are controlled by feedback loops, in much the same way that a thermostat controls the temperature in a room. The thermostat is set to a specific temperature, called a *set point*. It detects the temperature, and when the temperature falls below the set point, it turns the heat on. When the room temperature rises to the set point, it turns the heat off again, thus maintaining an even temperature. Homeostasis provides a flexible system for maintaining a set point in circumstances in which environmental conditions change. For example, if someone were to leave a window open on a cold day, the thermostat would keep the heat on longer in an attempt to maintain the temperature at the set point.

Homeostatic processes work inside the body. They control nearly all the body's operations so that when a drug is taken and it alters some aspect of the body's functioning, the body's response is controlled by a homeostatic mechanism. The disruption or disturbance created by the drug is detected, and this information is sent to the mechanism that controls the disrupted function. The control center responds by compensating for the effect of the drug and restoring normal functioning; that is, it returns the function to its set point. If the drug is repeatedly administered, the body gets better and better at restoring normal function and diminishing the disruptive effect of the drug. This means that the drug will have a smaller and smaller effect the more it is administered. Some

of these compensatory processes kick in quickly, but others take longer to develop. Thus, tolerance may appear rapidly to some drug effects and very slowly to others.

When drug administration is stopped and the drug's disruptive effect is removed, the compensatory process is discontinued because it is no longer needed. Again, some compensatory effects may disappear rapidly, but others may go away slowly. Weeks or months may be required for normal functioning to return.

General or Nonspecific Tolerance. To compensate for the effect of a drug, the body may use a variety of physiological mechanisms. Entire physiological systems may be involved, or the compensation may take place at the level of a single cell. For example, if a drug blocks a receptor at a synapse, the body might attempt to compensate for the blockage by creating more receptors so that the transmitter at the synapse can be restored to normal functioning. It might also cause more transmitters to be released from the presynaptic neuron to help overcome the blockage (Nutt, 1997) (see Chapter 4). These changes in sensitivity that take place at the drug's site of action are equivalent to metabolic tolerance because when they occur, all other effects of the drug are diminished to the same extent and may be thought of as *general* or *nonspecific* tolerance.

Specific Tolerance. Physiological adaptations may also take place in any other system in the body that the drug disrupts either directly or indirectly and may be mediated by any number of diverse compensatory mechanisms. If a drug lowers body temperature, for example, the body may use a number of different mechanisms to raise body temperature. These could include altering the metabolic rate or changing the rate of heat loss through the skin by decreasing blood flow to the skin. Because this tolerance is specific to a particular drug effect, it may develop independently of other tolerance mechanisms that may be taking place at the same time and may develop or disappear at different rates.

Functional Disturbances

Constantine Poulos and Howard Cappell (1991), at the Addiction Research Foundation of Toronto, have pointed out that one implication of homeostatic theory is that tolerance will develop only when a drug effect causes a disruption in homeostasis and the disruption is of some significance to the organism. For example, we know that (a) amphetamine causes *anorexia* (loss of appetite) in rats and that (b) this effect will show tolerance when the drug is repeatedly administered to hungry rats in the presence of food. Tolerance to anorexia, however, will not develop if the amphetamine is given repeatedly to rats after they have been fed or given to hungry rats when there is no food available to eat. In other words, no tolerance to the anorexic effect of amphetamine will develop in rats that are not interested in eating or do not have the opportunity to eat at the time they receive the drug. The anorexic effect of the drug does not have a chance to interfere with the functioning of the organism, and there is no feedback to the feeding control mechanism. Similarly, tolerance to the *hypothermic* (body-cooling) effect of alcohol does not develop in rats in a very warm environment, where alcohol does not have a hypothermic effect, and tolerance to the *analgesic* (pain-relieving) effect of morphine develops faster in rats that are subjected to painful stimuli after being given the drug (Poulos & Cappell, 1991). In other words, tolerance will develop (or will develop much faster) only in a circumstance where a drug places a demand on an organism's homeostatic mechanisms. Tolerance to drug effects that are not detected or that do not disrupt functioning does not develop.

Behavioral Tolerance

It has often been demonstrated that tolerance can be influenced by learning and conditioning processes. In other words, through experience with a drug, an organism can learn to decrease the effect that the drug is having. This is called *behavioral tolerance*. This learning, which can involve both instrumental and respondent conditioning

processes, is extensively discussed later in this chapter. For now, it is necessary to have a good understanding of how certain types of drug effects become conditioned to environmental stimuli.

WITHDRAWAL SYMPTOMS AND PHYSICAL DEPENDENCE

Withdrawal symptoms are physiological changes that occur when the use of a drug is stopped or the dosage is decreased. Different drugs produce different withdrawal symptoms, but drugs of the same family generally produce similar withdrawal. Withdrawal can be stopped almost instantly by giving the drug that has been discontinued. Often another drug of the same family will also stop withdrawal. This phenomenon is known as *cross dependence*.

Withdrawal usually begins some hours after the use of a drug has been stopped, but it can be produced much more quickly by giving an antagonist drug. Naloxone, a powerful antagonist to morphine, rapidly blocks all morphine effects soon after it is given. When naloxone is given to morphine-dependent humans or nonhumans, severe withdrawal can be seen in minutes.

Probably no word in the field of drug research causes more misunderstanding or has been abused more than *dependence*. It is generally used in two ways: (a) to describe a state in which discontinuation of a drug causes withdrawal symptoms and (b) to describe a state in which a person compulsively takes a drug.

At one point, it was believed that the two states were exactly the same. It was assumed that if you took a drug to the point that withdrawal symptoms would occur when you stopped, you were "dependent," and you would then be driven to seek out and consume the drug in a compulsive manner in order to avoid withdrawal. We now know that this assumption is not correct, but the word *dependence* is still used incorrectly as an explanation for drug abuse. This aspect of dependence will be discussed in more detail in Chapter 5.

More recently, it has been recognized that people will compulsively use drugs that do not cause unpleasant withdrawal symptoms. The term *psychological dependence* is sometimes used to describe this, and the terms *physical dependence* and *physiological dependence* are used to refer only to the state in which withdrawal symptoms occur if the use of a drug is discontinued. This text uses the terms *dependence, physical dependence*, and *physiological dependence* interchangeably to indicate a state in which withdrawal symptoms will occur. Psychological dependence is discussed more thoroughly in Chapter 5.

Tolerance and dependence are believed to be closely related. Withdrawal symptoms are usually thought of as expressions of the adjustment that the body has made to a drug. As described earlier, with repeated administration of a drug, the body changes its functioning and uses homeostatic feedback to compensate for the physiological changes the drug produces. Later, when the drug is discontinued and its effects disappear, it takes some time for the body to readjust to its absence. This readjustment is expressed in the form of withdrawal symptoms. For this reason, the physiological changes seen in withdrawal are usually opposite to the effects of the drug. For example, constipation is one of the more marked effects of heroin use, and one of the major symptoms of withdrawal from heroin is diarrhea.

This sort of idea was first formulated by Solomon and Corbit (1974), who were proposing a theory of addiction and were interested in the *hedonic*, or pleasurable, effects of drugs as an explanation of their use. They hypothesized that drugs of abuse create a highly pleasurable state by a mechanism they called the *A process*. A short time after the A process is initiated by taking the drug, a compensatory unpleasant state is created. They called this the *B process*. Because the state created by the A process is pleasurable and the state created by the B process is unpleasant, they tend to cancel each other. This explains tolerance to drug-induced pleasure. Because the B state lasts longer than the A state, there is a period after the A process ends when the B state dominates, and this causes unpleasant symptoms that we experience as withdrawal. This process is described in Figure 3-1.

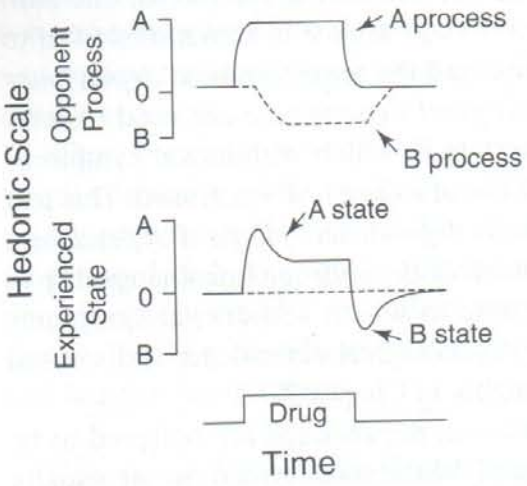


Figure 3-1 The upper panel shows the drug effect on the A process and the opposing B process separately. After the drug is given, the A process increases, but shortly after that, the opposite B process begins. When the drug wears off, the A process diminishes, but the B process continues for a while before disappearing. The lower panel shows the result of combining the A and the B effect. It shows that the A effect will be strongest right after the drug is taken and then diminish. This decreased effect is what would be called acute tolerance. The B effect dominates after the drug has worn off. The B effect would be experienced as a hangover or withdrawal effect. Solomon and Corbit originally proposed this mechanism to explain changes in pleasure (hedonic state) caused by a drug, but the idea can be used to explain many drug effects. Adapted from Solomon and Corbit (1974).

Although Solomon and Corbit's theory was formulated to explain hedonic states created by drugs, it can be applied to understanding any effect of a drug where the A state is any drug effect and the B state is an opposite, compensatory effect.

Hangover. *Hangover* is a term that is used in different ways. It usually refers to the aftermath of the acute effects of a drug, such as when you go out drinking at night and then feel sick the next day. Often a hangover can be thought of as brief withdrawal symptoms that arise from acute tolerance. Thus, when you take a drug, its effect increases as the blood level increases, but often the effect diminishes faster than the level of the drug in the blood (acute tolerance). This decrease is due to the development of acute tolerance as described earlier. Solomon and Corbit developed the model to describe long-term use of a drug, so that the period of drug administration in the diagram might correspond to a period of weeks or months of continuous use, and the B state at the end of drug use would be unpleasant withdrawal. The process works just as well to describe a single drug administration where the B state as the drug wears off, would be a hangover.

An example of the effect described by Solomon and Corbit within a single administration of the tranquilizer chlordiazepoxide is shown in Box 3-1, where the A process is the tranquilizing (*anxyolytic*, or *anxiety-relieving*) effect of the drug chlordiazepoxide and the B process is the opposite: anxiety.

If withdrawal and hangover are expressions of compensatory effects that cause tolerance to drugs, you might expect there to be a strong correlation between tolerance and withdrawal symptoms. There is not; it is not unusual for a person to show considerable tolerance to the effects of a drug but to have no withdrawal symptoms when the drug is discontinued. Alcohol is a good example. Many longtime drinkers have a considerable tolerance for some of the effects of alcohol but do not show any signs of physical dependence. There are a number of reasons why this could be so. To begin with, there maybe some tolerance, like behavioral tolerance, that is not created by a physiological compensatory effect, and so there would be no physiological withdrawal. In addition, withdrawal symptoms may not be experienced if the rate of elimination of the drug from the body is very slow, as with THC, the active ingredient in marijuana (see Chapter 15). With slow elimination, the body may be able to "readjust" at the pace of the drug's elimination, and withdrawal symptoms may not be expressed.

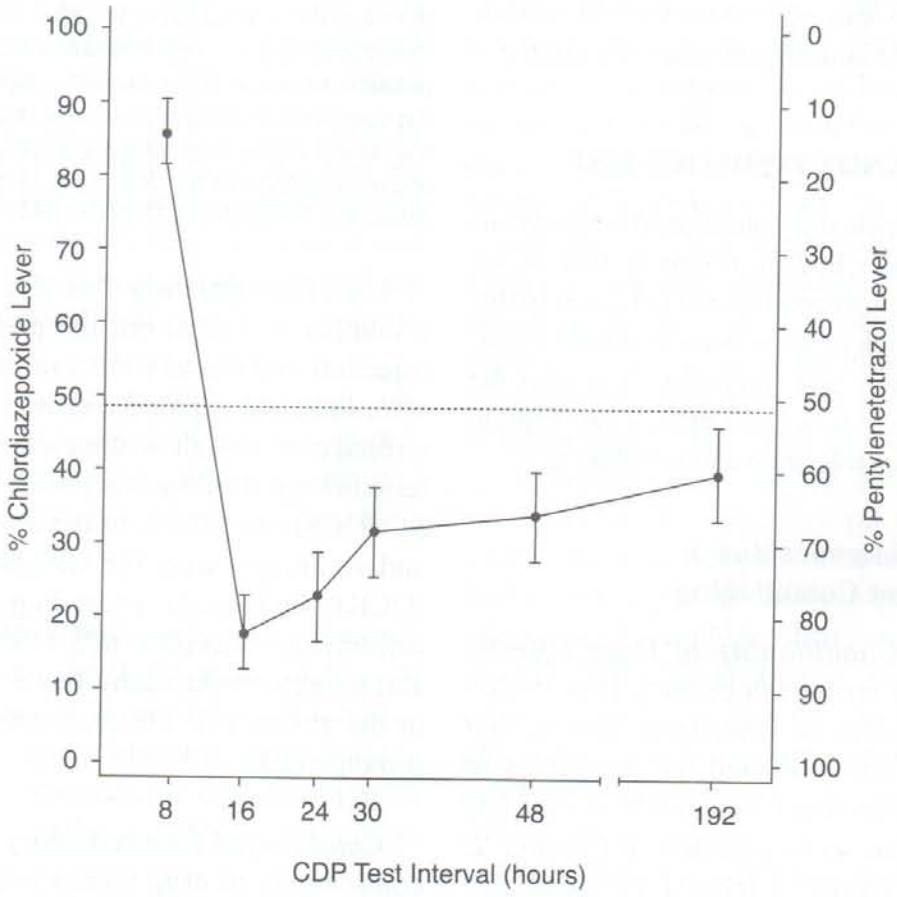
Withdrawal symptoms may vary in intensity from one drug to another. With some drugs, withdrawal symptoms may be so slight that they can be detected only by using sensitive instruments, and the individual might not notice them. With other

BOX 3-1 Anxiety as a Conditioned Compensatory Response to a Tranquilizer

Using a two-lever, drug discrimination procedure, Barrett and Smith (2005) of Vanderbilt University in Nashville, Tennessee, trained rats to discriminate between a dose of chlordiazepoxide (CDP) and a dose of pentylenetetrazol (PTZ). Chlordiazepoxide is a benzodiazepine tranquilizer that relieves anxiety and has a calming effect (it is an anxiolytic). It works by enhancing the effect of the inhibitory transmitter GABA. Pentylenetetrazol has exactly the opposite effect; it reduces the effects of GABA and causes tension and anxiety (it is an anxiogenic) (see Chapter 7). Barrett and Smith trained their rats to press one lever after being injected with CDP, that is, when they were calm and relaxed, and the second lever after being injected with PTZ, that is, when they were tense and anxious. After being given saline, the rats distributed their responding equally between the two levers.

They then gave their rats an injection of chlordiazepoxide and tested them in the two-lever apparatus at various times after the injection. As can be seen in the diagram below, 8 hours after the CDP injection, rats made 90 percent of their responses in the CDP lever, but by 16 hours after the injection, they made most of their responses on the PTZ lever. Responding slowly returned to the 50 percent level over the next few hours.

What appeared to be happening was that 8 hours after the CDP injection, the rats still felt calm and relaxed and responded on the CDP lever, but all this time, a compensatory response had been developing that was opposite to the CDP effect. After the drug had left the system, the



(*Continued*)

BOX 3-1

compensatory response remained. This made the rats anxious and tense, a feeling like that produced by PTZ, so they pressed the PTZ lever at the 16-hour test. Eventually, this compensatory response diminished, and by 48 hours the rats returned to drug-free response levels, 50 percent on each lever.

It is this sort of process that seems to be responsible for hangovers to many drugs and makes it so that drugs, after they have worn off, sometimes have an effect opposite to their normal effect.

This experiment illustrates the Solomon and Corbit theory described in the text. The A process is the tranquilizing effect of the CDP, and the B process is compensatory anxiety. Compare the lower panel of Figure 3-1 with this Figure.

drugs, withdrawal can be so severe as to cause death. The extent of withdrawal may also depend on the dose and administration schedule of the drug. Drugs that are taken intermittently may cause hangover each time they are taken but are unlikely to create withdrawal when their use is discontinued.

Later in this chapter, we will discuss how withdrawal symptoms can be conditioned to stimuli associated with the administration of the drug.

TOLERANCE AND CONDITIONING

In Chapter 2, we looked at conditioned behaviors as dependent variables in drug research; that is, we asked how drugs affect conditioned behavior. In this section, we will look at some ways in which conditioning, both operant and respondent, can alter the effects of drugs and how such effects can explain phenomena such as tolerance and withdrawal.

Behavioral Tolerance Based on Respondent Conditioning

Respondent Conditioning of Drug Effects. At the end of the nineteenth century, Ivan Pavlov and his colleagues in St. Petersburg, Russia, first discovered and demonstrated the principles of respondent conditioning (also known as classical conditioning) that were outlined in Chapter 2. Researchers in Pavlov's laboratory were also the first to show that the effects of a drug could be conditioned to neutral stimuli present at the time the drug was having its effect. One of these experiments was conducted in the following manner:

> A dog was given a small dose of apomorphine subcutaneously and after one to two minutes a note of definite pitch was sounded during a considerable time. While the note was still sounding the drug began to take effect upon the dog: the animal grew restless, began to moisten its lips with its tongue, secreted saliva and showed some disposition to vomit. After the experimenter had reinforced the tone with apomorphine several times it was found that the sound of the note alone sufficed to produce all the active symptoms of the drug, only in a less degree [experiments by Podkopaev]. (Pavlov, 1927, p. 35)

Placebo?

Later the researchers were able to show that after a number of injections, the preliminaries to the injection and the administration procedure itself were sufficient to produce salivation and other drug effects, even though no drug was given. In Pavlov's terminology, the drug was the *unconditioned stimulus* (UCS); the effects of the drug—the salivation and vomiting—were the *unconditioned response* (UCR); the stimulus preceding the drug was the *conditioned stimulus* (CS); and the salivation and nausea produced by these stimuli presented in the absence of the drug was the *conditioned response* (CR).

Conditioned Compensatory Responses. The conditioning of drug effects is more complicated than it would appear at first because the unconditioned response and the conditioned response to

the drug are not always the same. Sometimes the stimuli paired with a drug (the conditioned stimulus), when presented in the absence of the drug, produce a physiological response (conditioned response) opposite to that produced by the drug (the unconditioned response). For example, it has been shown in rats that an unconditioned response to morphine is analgesia (a decreased responsiveness to painful stimuli), whereas the conditioned response to stimuli repeatedly paired with morphine injections is *hyperalgesia* (an increased sensitivity to pain). The reasons for this are complex but can be understood if you realize that what is being conditioned is often not the effect of the drug itself but the body's attempt to resist the effect of the drug (Eikelboom & Stewart, 1982).

Earlier it was shown that the body resists drug-induced changes by making adjustments or compensatory changes in its physiology in an attempt to restore normal functioning. These compensations make the body less susceptible to the drug when it is given later, and they are responsible for tolerance. It appears that in many cases, these compensatory responses, not the initial effects of the drug, become conditioned to stimuli that are repeatedly paired with the administration of the drug. Because the compensatory response is in a direction opposite to that of the drug alone, the conditioned drug effect will also be opposite to the initial drug effect.

It is important to understand the nature of conditioned drug effects because they play an important role in how the effects of a drug are expressed when the drug is administered later. An example is conditioned drug tolerance.

Conditioned Drug Tolerance. Early research into tolerance and the development of conditioned compensatory responses to drugs was conducted at McMaster University by Shepard Siegel and his colleagues. Siegel investigated the development of tolerance to the analgesic effect of morphine. To test analgesia, he placed rats on a metal plate that was heated to 54 degrees Celsius. After a few seconds on this plate, rats normally lift a hind paw to their mouth as if they are licking it. This test is known as the *paw lick test*, and the measure of analgesia is the latency or the length of time the rat waits before licking (see Chapter 2). After an injection of morphine, the paw lick latency increases, indicating that the morphine has reduced the animal's sensitivity to pain. With repeated trials, the latency tends to get shorter and shorter as tolerance to the morphine develops (S. Siegel, 1975).

In his experiment, Siegel was able to demonstrate that rats would show tolerance to the analgesic effects of morphine only if they were given the paw lick test in the same room where repeated morphine injections had been experienced earlier. If they were given morphine in the colony room where they were normally housed and were tested in a different room, the animals had long latencies similar to those of animals that had never been given morphine. The tolerance to morphine was dependent on the environment in which the drug had been experienced.

To explain this effect, Siegel proposed that the environment repeatedly associated with the drug acts like a conditioned stimulus, but rather than becoming a conditioned stimulus for the effect the drug is having, it becomes a conditioned stimulus for the physiological changes the body is making to compensate for the effect the drug is having. Thus, the environment associated with the administration of the drug elicits physiological responses opposite to the effect of the drug. These changes help prepare the rat for the drug and diminish its effect; that is, they cause tolerance.

In support of his theory, Siegel was able to show that if he injected a rat with saline and gave it the paw lick test in an environment that had previously been associated with repeated injections of morphine, their latencies would get shorter than normal, that is, the animal would show *hyperalgesia* (an increased sensitivity to pain). This was the compensatory response that had been produced by the morphine environment through conditioning.

Box 3-2 gives an example of how this type of tolerance can protect humans and nonhumans from a heroin overdose.

BOX 3-2 The Mystery of Heroin Overdose

One of the greatest risks of being a heroin addict is death from heroin overdose. Each year about 1 percent of all heroin addicts in the United States die from an overdose of heroin despite having developed a fantastic tolerance to the effects of the drug. In a nontolerant person, the estimated lethal dose of heroin may range from 200 to 500 mg, but addicts have tolerated doses as high as 1,800 mg without even being sick (Brecher & the Editors of *Consumer Reports*, 1972). No doubt, some overdoses are a result of mixing heroin with other drugs, but many appear to result from a sudden loss of tolerance. Addicts have been killed by a dose that was readily tolerated the day before. An explanation for this sudden loss of tolerance has been suggested by Shepard Siegel of McMaster University and his associates Rily Hinson, Marvin Krank, and Jane McCully.

Siegel reasoned that tolerance to heroin was partly conditioned to the environment where the drug was normally administered. If the drug is consumed in a new setting, much of the conditioned tolerance disappears, and the addict is more likely to overdose. To test this theory, S. Siegel and his associates (1982) ran the following experiment. Rats were given daily intravenous injections for 30 days. The injections, either a dextrose placebo or heroin, were given in either the animal colony room or a different room where there was constant white noise. The drug and the placebo were given on alternate days, and the drug condition always corresponded with a particular environment so that some rats always received the heroin in the white-noise room and the placebo in the colony. For other rats, the heroin was always given in the colony, and the placebo was always given in the white-noise room. Another group of rats served as a control. They were injected in different rooms on alternate days but were injected only with dextrose and had no experience with heroin.

All rats were then injected with a large dose of heroin: 15 mg/kg. The rats in one group, labeled the ST group, were given the heroin in the same room where they had previously been given heroin. The other rats, the DT group, were given the heroin in the room where they had previously been given the placebo.

Siegel found that 96 percent of the control group died, showing the lethal effect of heroin on nontolerant animals. Rats in the DT group that received heroin were partly tolerant; 64 percent died. Only 32 percent of the ST rats died, showing that their tolerance was greater when the overdose test was done in the same environment where the drug had previously been administered.

Siegel suggested one reason for addicts' suddenly losing their tolerance: They take the drug in a different or unusual environment, like the rats in the DT group. Surveys of heroin addicts admitted to hospitals and diagnosed as suffering from heroin overdose tend to support this conclusion. Many addicts reported that they had taken the near-fatal dose in an unusual circumstance or that their normal pattern was different on that day (S. Siegel et al., 1982).

Conditioned Compensatory Responses and Withdrawal. Besides explaining some tolerance, learning processes may be responsible for some withdrawal symptoms. We have seen how compensatory responses may be conditioned to a particular environment where the drug is repeatedly given. Later, if an animal is placed in that environment without the drug, it will show conditioned compensatory responses—physiological changes opposite to the drug's effect. When they occur in the absence of the drug, they are withdrawal symptoms, as described earlier in this chapter; therefore, some aspects of withdrawal can be conditioned and may be evoked by specific

stimuli previously associated with the use of the drug (S. Siegel, 1983). For example, former heroin addicts who have gone through withdrawal just after they stop using a drug will frequently experience withdrawal symptoms again when they return to places where they have experienced the effects of the drug. As the following example illustrates, there can be little doubt that these conditioned withdrawal symptoms play an important part in relapse to drug use in postdependent addicts:

> The patient was a 28-year-old man with a ten-year history of narcotic addiction. He was married and the father of two children. He reported that, while he was addicted, he was arrested and incarcerated for six months. He reported experiencing severe withdrawal during the first four or five days in custody, but later he began to feel well. He gained weight, felt like a new man, and decided that he was finished with drugs. He thought about his children and looked forward to returning to his former job. On the way home after his release from prison, he began thinking of drugs and feeling nauseated. As the subway approached his stop, he began sweating, tearing from his eyes, and gagging. This was an area where he had frequently experienced narcotic withdrawal symptoms while trying to acquire drugs. As he got off the subway he vomited onto the tracks. He soon bought drugs and was relieved.
>
> The following day he again experienced craving and withdrawal symptoms in his neighborhood, and he again relieved the symptoms by injecting heroin. The cycle repeated itself over the next few days and soon he became readdicted. (O'Brien, 1976, p. 533)

The addict's eyes teared, and he began sweating when he came into the subway station, where he had previously acquired drugs. It is likely that his body was preparing itself for an injection of heroin, which it had become conditioned to expect in that environment.

This example shows that conditioned withdrawal symptoms do not disappear when the body makes its initial readjustment to the absence of a drug. Conditioned withdrawal symptoms will go away only through the process of extinction, that is, the presentation of the stimuli when they are not followed by the drug.

Importante para tratamento!!

Behavioral Tolerance Based on Operant Conditioning

An early experiment in this area was done by Judith Campbell and Lewis Seiden (1973) at the University of Chicago. They trained rats to respond for food reinforcement in a Skinner box on a *differential reinforcement of low rates* (DRL) schedule. On a DRL schedule, the animal is reinforced only if it waits for a fixed period of time between responses. In other words, it is reinforced for responding at a low rate. When amphetamine is given, it stimulates responding, and the rat loses reinforcements because it cannot wait long enough between responses.

For 28 sessions, Campbell and Seiden gave amphetamine to one group of rats immediately before placing them in a Skinner box where they were reinforced on a DRL schedule. Another group of rats was given the same number of injections and the same number of sessions on the DRL schedule, but the amphetamine was given after the DRL trials. Over the period of the experiment, the amphetamine-pretreated rats developed tolerance and were able to obtain more and more reinforcements, but when the other rats were tested on the DRL with amphetamine, they performed as though they had never received the drug; they had no tolerance. If the tolerance shown by the first group had been the result of metabolic or physiological changes that develop in response to the presentation of the drug alone, it should have shown up in both groups because both groups received the same exposures to the amphetamine.

Campbell and Seiden concluded that the difference had only one explanation: The rats had learned to alter their behavior to compensate for the change that the amphetamine caused. This interpretation was supported by the observation that no tolerance develops to the rate-increasing effect of amphetamine on fixed interval (FI) responding (Schuster, Dockens, & Woods, 1966). Increased responding on the FI does not cause the rat to lose reinforcements, whereas it does on the DRL schedule. Thus, it appeared that the rats had developed a particular strategy for overcoming

the effect of the amphetamine on DRL. This strategy was learned because it was reinforced by an increase in food presentations.

A similar hypothesis was tested by Muriel Vogel-Sprott (1992) and her colleagues at the University of Waterloo, who have done considerable research on the development of behavioral tolerance to the effects of alcohol on humans. They used a different technique. They reasoned that if tolerance was a result of learning strategies to compensate for the effect of a drug, then the development of tolerance should depend on the occurrence of a reinforcement when a compensatory response is made.

In her experiments, human subjects are trained on a cognitive or motor task such as the pursuit rotor until their performance is stable. Then they are given alcohol for a number of sessions, and this interferes with their performance. Typically, Vogel-Sprott has one group of subjects who are told that they will be given a 25-cent reward immediately after each trial in which they are able to resist the disruptive effects of alcohol and perform in their normal, drug-free range. A second group of subjects is also given a 25-cent reward for each such trial, but the money is saved up and given at the end of the session, and no information is given about which trials were in the drug-free range. A third group is not given any information or money.

Vogel-Sprott has repeated this experiment many times and always finds that subjects given information or feedback about their performance, whether they are given money or not, always develop tolerance rapidly, and the other groups develop tolerance slowly, if at all (Vogel-Sprott, 1992). It seems that in her experiments, the subjects' knowledge that they are resisting the effects of alcohol is sufficient reinforcement for learning to resist the effects of the alcohol.

The Campbell and Seiden and the Vogel-Sprott studies can be understood in terms of homeostatic theory. In the Campbell and Seiden study, the disruptive effects of the amphetamine caused a loss of reinforcements; consequently, the drug effect had functional significance for the rat. As a result, a homeostatic mechanism kicked in, and a compensatory response was acquired that permitted the animal to respond more slowly and receive more food. No compensatory response developed to the FI responding because the effect of the drug (an increased response rate) did not cause the animal to lose reinforcements and had no biological significance. Similarly, in the Vogel-Sprott experiment, the effect of the alcohol on the pursuit rotor task had no significance for the subjects in the control group, who were not informed that the alcohol was having an effect. The subjects in the experimental group who were paid for good performance, however, found that the disruptive effect of the alcohol had significance for them, and so tolerance developed. Box 3-3 gives an example of how tolerance to alcohol could have played a role in the crash that killed Princess Diana.

BOX 3-3 Did Alcohol Kill Princess Diana?

On August 31, 1997, the world was shocked to learn that Britain's Princess Diana was killed in a car crash in a tunnel in Paris. The reasons for the deadly crash have never been clearly established, but a contributing factor could have been that Henri Paul, the driver of the princess's car, had a blood alcohol level of 175 mg/100 ml of blood—three times the legal limit. Under other circumstances, an accident like this might have been clearly blamed on the intoxicated state of the driver, but the blame is not so readily placed in this case. Diana's car was speeding in an attempt to avoid photographers who were chasing it in other cars and on motorcycles. Reports of witnesses say that Henri Paul "seemed fine" when he took the wheel that night. In fact, videotapes from security cameras in Diana's hotel show Henri Paul walking quite normally, carrying on conversations, and showing no signs of intoxication.

What we know about the development of tolerance to drugs might explain why Henri Paul could "seem fine" and still have such a high level of alcohol in his blood.

Given the reports that Henri Paul had a history of heavy drinking, it is likely that he had developed a considerable tolerance to many of the direct effects that alcohol had on his nervous system (physiological tolerance). In addition, on that day, he had not expected to be called back to work, and he seems to have started drinking early in the morning. He probably had been drinking continuously for an extended period of time. Under these circumstances, extensive acute tolerance has a chance to develop. It may not be surprising, then, that Henri was able to show normal behavior even though his blood alcohol level was excessive.

If Henri Paul was that tolerant, could alcohol have played a role in the accident?

It seems so. To begin with, we know that tolerance does not develop to all the effects of a drug at the same time, and it is possible to be tolerant to some effects of a drug and not others. All we know is that Henri Paul was able to walk and talk normally. On the basis of the work of Vogel-Sprott, we know that tolerance to an effect of alcohol develops if the individual is provided with feedback on the effect of alcohol and is reinforced for making a compensatory response to overcome alcohol's effect. Walking and talking are behaviors that most people who drink regularly are able to practice under the influence of alcohol; very often those behaviors are rewarded with social approval. Because Henri Paul was a professional driver, it would have been disastrous for him to exhibit any effects of alcohol intoxication before driving. Therefore, walking and talking were likely to be the first behaviors restored by both acute and chronic tolerance.

The effects of alcohol on driving might also be subject to learning compensatory strategies that cause tolerance. Indeed, in Vogel-Sprott's laboratory, research on a driving simulator shows such an effect. Diana's driver might possibly have been able to drive safely under normal driving conditions. In fact, he may have done so many times. But it is unlikely that Henri Paul had had a chance, while intoxicated, to practice the skills required to race through a tunnel at high speed in an effort to elude photographers. Such skills may not have had a chance to develop, regardless of his tolerance to all other effects of alcohol.

That fateful night, alcohol may have had a big effect on Henri Paul, but because of his tolerance to some effects, no one, not even Henri Paul himself, was able to detect the debilitating effect. In fact, under most circumstances, it would have gone undetected.

Driving is a complex task requiring many different cognitive and motor skills. In addition, the demands that will be made on a driver on any particular trip cannot be predicted. A person may be able to drive a car safely at a given blood alcohol level, provided that nothing unusual happens. But a driver can never know what demands will be made and whether alcohol, even at a low dose, will be responsible for an accident.

SENSITIZATION

Most of the time, when a drug is repeatedly administered, tolerance to the many effects of the drug develops. In some circumstances, however, an effect of a drug can increase with repeated administrations. This is known as *sensitization* or *reverse tolerance*.

Sensitization is much less common than tolerance, and much less is known about it. Most of what we know about sensitization comes from studies of the activating effects of a variety of drugs, including cocaine, amphetamine, nicotine, alcohol, phencyclidine, and opiates such as morphine. At low doses, all these drugs produce an activating effect when first given to laboratory animals. This effect is characterized by increased motor activity and rearing behavior in rats. At high doses, *stereotyped behaviours* are seen. Stereotyped behaviors are repetitive movements, such as head bobbing and sniffing, that are engaged in for extended

periods of time. When repeated low doses are given, there is a progressive increase in activation with each administration. Repeated administration of higher doses will eventually cause stereotyped behavior where only activation was caused by the initial dose (T. E. Robinson & Berridge, 1993, p. 256).

Like tolerance, this sensitization may also be conditioned to a particular environment (J. Stewart & Badiani, 1993). This has been demonstrated in two different ways. First, it has been shown that, as with tolerance, if sensitization is created by repeatedly administering the drug in a specific environment, then sensitization will be greatly diminished or will not appear at all when the drug is given in a different environment. Second, if sensitization results from repeated injections in a specific environment, then that environment will act as a conditioned stimulus for a drug-like conditioned response. In other words, if you place an animal in the environment after a placebo injection, it will show increased activity—the same response that the drug causes (T. E. Robinson & Berridge, 1993, p. 259; P. B. Silverman & Bonate, 1997, p. 124). In this regard, sensitization appears to be a mirror image of tolerance, except that the conditioned response is a drug-like response rather than a drug-opposite response. When the drug-like conditioned response (activation) is elicited in conjunction with the drug effect (also activation), there is an enhanced drug effect.

In some circumstances, sensitization may also be produced by operant conditioning processes. We saw that Vogel-Sprott was able to cause tolerance to the disruptive effect of alcohol by paying subjects to resist the effects of alcohol on a motor task. She was also able to increase the effects of alcohol by giving subjects money when their performance was further disrupted by alcohol (Zack & Vogel-Sprott, 1995).

Cross sensitization can also be demonstrated. Laboratory animals with a sensitization to morphine will also show increased activation to cocaine and amphetamine and vice versa. In fact, it has been found that stress will also sensitize a rat to the activating effect of many of these drugs (Piazza & Le Moal, 1998).

Sensitization may differ from tolerance in the fact that it seems to be very persistent. Sensitization conditioned to a particular environment and nonconditioned sensitization have been seen as long as a year after drug exposure in rats (during one-third of their lifetime), and there are no reports of it dissipating over time. In fact, there is evidence that it might *increase* with time (T. E. Robinson & Berridge, 1993, p. 258; P. B. Silverman & Bonate, 1997, p. 125).

From the considerable work directed at discovering the brain mechanisms responsible for the sensitization of behavioral arousal, it has become evident that no single neuronal effect can be responsible (R. C. Pierce & Kalivas, 1997). Sensitization clearly involves the brain's general motivation control system, which is centered in the limbic system. It is responsible for arousal and approach to both conditioned and natural incentives or motivating stimuli such as food and receptive sexual partners. The part of this system that becomes sensitized is the *mesolimbic dopamine system*. As we shall see in Chapters 4 and 5, this mechanism also appears to be responsible for the reinforcing effects of drugs. Sensitization of this system has been proposed as an explanation for drug abuse (T. E. Robinson & Berridge, 2000).

Sensitization of drug-induced activation has not been demonstrated in humans, but sensitization has been linked to the ability of drugs like cocaine and amphetamine to produce symptoms of psychosis in heavy users (see Chapter 11).

EXPECTANCY AND CONTEXT

It is becoming clear that the context in which a drug is administered is capable of having a significant influence on the effect that the drug will have. One of the most powerful contextual effects is whether you know whether the drug is being administered at all, that is, whether you are expecting a drug effect. This the *placebo effect*, and it was discussed in Chapter 2 in a discussion of research design. In recent years the placebo effect has become the

subject of considerable interesting research. In 1995 a study was published by Benedetti, Amazino, and Maggi, researchers at the University of Turin Medical School in Italy (Colloca & Benedetti, 2005). They were investigating the effect of the drug promulgide on pain in human subjects. Their results showed that promulgide was better at relieving pain than a placebo and that a placebo was better than no treatment al all. This is not surprising, and these results would normally be interpreted as indicating that promulgide was an effective painkiller, but these researchers included an unusual treatment group in their research. They had a group of participants receive an injection of promulgide through an infusion pump without knowing that they had received any drug at all. Interestingly, in this group, promulgide had no effect on pain. The entire effect of the drug depended on the participants knowing that they were getting the drug. But if all the pain relief was a placebo effect, why did the drug have a stronger effect than the placebo alone?

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Colloca and Benedetti explained the effect this way: They proposed that there is a "top-down" pain-relieving pathway from the cortex to a pain control center in the lower brain that is capable of blocking pain when activated. When a person knows that a drug is being administered, this pathway is activated, and pain is diminished. They called this the *expectation mechanism* and it is the reason for the placebo response. They proposed that the promulgide in their experiment had no direct effect on pain. Rather, it directly stimulated this expectation mechanism, and placebo response was enhanced. This is why the promulgide group showed a greater response than the placebo alone.

There are other examples of how the context in which a drug is given can alter the effect of a drug. For example, Volkow and colleagues (2003) used PET scans to measure glucose metabolism (see Chapter 4) and showed that the effect of an injection of methylphenidate (a drug that has similar effects as cocaine) increased glucose metabolism in some parts of the brains of cocaine abusers. Interestingly, the effect was twice as great if the participants were expecting the drug than if they were not expecting the drug. In addition, Volkow and her associates showed that self-reports of being "high" were also about 50 percent greater when the drug was expected. Their PET scans showed that the increased response in those expecting the drug was probably due to an increased activity in the thalamus.

It has also been shown that drugs may have different effects when they are self-administered than when the person or laboratory animal has no control over the drug administration. Hemby, Koves, Smith & Dworkin (1997) showed that levels of dopamine in the nucleus accumbens (a part of the mesolimbic dopamine system) was higher in rats that were allowed to push a lever to give themselves injections of cocaine than in yolked control rats that received an injection every time the rats in the self-administration group gave themselves an injection.

Novel Environments. It is also clear from research on nonhumans that many drug effects are different when the drug is administered in a novel environment. As discussed in the previous section, stimulant drugs like cocaine and amphetamine tend to cause increases in motor behavior after they are administered, and with repeated administration, this effect shows sensitization. Recent research has shown that if the drug is administered in a novel environment, the amount of locomotor stimulation is considerably more than would be seen if the drug had been administered in a familiar setting. In addition, sensitization of this effect is much more rapid and can be induced at a lower dose if the drug is given in a novel setting. Investigations of this effect have shown that when these drugs are administered in a novel setting, they actually have different effects on the nervous system, effects that are likely to make them more addictive (Badaiani & Robinson, 2004).

CHAPTER SUMMARY

- Tolerance is defined as (a) the decreased effectiveness (or potency) of a drug that results from repeated administrations or (b) the necessity of increasing the dose of a drug in order to maintain its effectiveness after repeated administrations.

- Tolerance develops and dissipates to different effects of drugs at different rates, and so it is likely to be the result of many different processes.
- There are a number of different mechanisms that can cause tolerance. These include metabolic tolerance, changes in metabolism of the drug's physiological tolerance, changes in the physiology to compensate for the effect of the drug, and behavioral tolerance, or conditioned changes in behavior that compensate for the effect of the drug,
- Much tolerance arises from homeostatic mechanisms, but it will develop only where the effect of the drug has some biological significance to the organism.
- Dependence is when withdrawal symptoms occur when the use of the drug is stopped or decreases. For many drugs, withdrawal symptoms will occur when the use of the drugs is stopped. Withdrawal symptoms are thought to be the expression of the compensatory (opposite) effect of the drug, expressed in the absence of the drug.
- Hangover can be thought of as an acute withdrawal symptom.
- Pavlov was the first researcher to demonstrate that stimuli, if paired with the administration of a drug a sufficient number of times, will eventually come to elicit some of the effects of the drug through classical conditioning processes. Later research has shown that, quite often, the effect that becomes conditioned is a physiological response opposite to the unconditioned effect of the drug. It appears as though the compensatory response becomes conditioned.
- Stimuli that are always present when a drug is given will come to elicit conditioned compensatory responses that diminish the effect of the drug. This tolerance does not occur when the drug is given in the absence of these stimuli. When a placebo is administered in the presence of stimuli that predict the drug, a drug compensatory response is sometimes seen. These conditioned compensatory responses are expressed as conditioned withdrawal.
- It has been demonstrated that if a drug interferes with the ability of an organism to obtain reinforcement, tolerance will develop quickly. If there is no reinforcement for compensating for the effect of a drug, tolerance may not develop. Similarly, tolerance to some effects develops only if the organism is reinforced for showing drug compensatory responses.
- Sensitization occurs where a drug effect increases with repeated administrations. Sensitization can be conditioned to specific environments. Sensitization occurs to only some effects of some drugs. These include increases in activity caused by reinforcing drugs, increased stereotyped behaviors caused by psychomotor stimulants, and the reinforcing effects of a drug.
- The expectations of experimental subjects can have a great influence on the effect of a drug. This is the placebo effect. Brain pathways that mediate the expectancy effect have been identified.
- The context in which a drug is administered can also influence its effect. This includes whether the drug is self-administered and whether it is administered in a familiar or a novel environment.