TWO

Prior to beginning work on this discussion, read the required chapters from the text and review the required articles for this week. Alcohol and caffeine have nearly opposite effects on behavior and the nervous system, yet these substances are not used to treat overdose or addiction to the other. Why not use caffeine to treat alcohol addiction? Analyze the issues of pharmacological and physiological antagonism. Explain the receptor systems involved and the central nervous system structures effects with regard to this question. Frame your analysis in terms of drug action first and other consequences second.

Text

Advokat, C. D., Comaty, J. E., & Julien, R. M. (2018). *Julien's primer of drug action: A comprehensive guide to the actions, uses, and side effects of psychoactive drugs* (14th ed.). Retrieved from https://vitalsource.com

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Book Resource

CHAPTER 6

Caffeine and Nicotine

CAFFEINE

Caffeine is the most widely consumed psychoactive drug in the world; in the United States, it is consumed daily by up to 80 percent or more of the adult population (Childs and deWit, 2012). It belongs to a family of substances called *xanthines* that also includes theophylline and theobromine. These substances stimulate the central nervous system, act on the kidneys to produce diuresis (urine), stimulate cardiac muscle, and relax smooth muscle.

Caffeine occurs naturally in the coffee bean (which is actually a seed) (*Coffea arabica* from Arabia), the tea leaf (*Thea sinensis* from China), the kola nut (*Cola nitida* from West Africa), and the cocoa bean (*Theobroma cacao* from Mexico). Tea actually contains more caffeine than coffee by dry weight but, because it is brewed more weakly, there is less caffeine in a standard serving. (In 1688, the Dutch began the cultivation of coffee on the island of Java. It is this association with coffee production that led to the nickname "java" for a good cup of coffee!) The reason why caffeine is found in so many (at least 60) plants is not known for certain, but it is speculated that it serves as a pesticide, because caffeine is toxic to the larvae of several insects. In addition to insects, caffeine is toxic to birds, dogs, and cats.

In addition to these organic sources, caffeine is often added to soft drinks, bottled water, candies, and medications (Table 6.1). In particular, since the introduction of the energy drink Red Bull (in Austria in 1987 and the United States in 1997), many other brands of energy drinks have been marketed, containing about 80 milligrams of caffeine per serving with a range of 50 milligrams to 550 milligrams per can or bottle, although they may not list the caffeine content on the label (Ishak et al., 2012; Sepkowitz, 2013; see Torpy and Livingston, 2013, for a table of caffeine content in energy drinks and other beverages).

TABLE 6.1 Caffeine content in beverages, foods, and medicines

Tea (6 oz.)	
Black tea	25–110 mg
Oolong tea	12–55 mg
Green tea	8–16 mg
Coffee (8 oz.)	
Brewed	135–150 mg
Instant	60–100 mg
Decaffeinated	1–25 mg
Sodas (12 oz.)	
Coke	46 mg
Pepsi	38 mg
Jolt	59 mg
Mountain Dew	52 mg
Surge	52.5 mg
Other	
Chocolate bar (50 gm)	20 mg
Cocoa (5 oz.)	2–20 mg
Hot chocolate (220 mL)	4 mg
Vivarin (1 tablet)	200 mg
Espresso drinks	
Latte	70 mg

AeroShot Pure Energy, the first caffeine mist product available to consumers, came in a small tube—resembling an asthma inhaler—and gave a 100-milligram shot of caffeine as well as assorted B vitamins when inhaled. It was recommended to be used no more than three times per day. As a dietary supplement, AeroShot didn't

require FDA approval, but the FDA issued a warning letter in March of 2012 about its dangers. In comparison, the average cup of coffee contains about 135 milligrams and, among regular caffeine users, daily intake averages between 200 and 500 milligrams, correlating with two to five cups of coffee daily.[1]

The Food and Drug Administration (FDA) classifies caffeine as "generally recognized as safe," but only in beverages containing up to 0.02 percent caffeine. Yet caffeine powder, which is sold as a dietary supplement, is unregulated. The FDA's official stance is that up to 400 milligrams per day of caffeine is safe for consumers. To date, caffeine may be added to beverages and food as long as it is listed in the ingredients panel, although the amount of caffeine is not required to be stated.

Ironically, in 1911, the FDA seized 40 kegs and 20 barrels of Coca-Cola syrup because the caffeine was considered a significant health hazard. By that time, the cocaine and alcohol had already been removed. The case dragged on for years until Coca-Cola eventually reduced the amount of caffeine and the legal action was dropped (Sepkowitz, 2013).

Pharmacokinetics

Taken orally, caffeine is rapidly and completely absorbed. Significant blood levels are reached after oral ingestion in 15 to 20 minutes and 99 percent is taken up within 45 minutes (Persad, 2011). Caffeine is soluble in both water and oil; therefore, it is equally distributed throughout the body and the brain and, like all psychoactive drugs, freely crosses the placenta to the fetus.

Caffeine's elimination half-life varies from about 2.5 to 10 hours (Magkos and Kavouras, 2005) and is extended by alcohol and other medications, in infants, women taking oral contraceptives, pregnant women, the elderly, and patients with chronic liver disease. Conversely, in cigarette smokers, caffeine's half-life is shortened; however, when smoking is terminated, caffeine's half-life increases. The reduced metabolism of caffeine can increase plasma caffeine levels and may contribute to cigarette withdrawal symptoms in heavy coffee drinkers, particularly because caffeine can induce or intensify anxiety disorders such as panic disorder (Lambert et al., 2006).

The structure and metabolism of caffeine are shown in Figure 6.1. The two major metabolites of caffeine, paraxanthine and theophylline, behave similarly to caffeine; a third metabolite, theobromine (the main alkaloid in chocolate), does not. Because theophylline relaxes the smooth muscles of the bronchi, it is used to treat asthma. Caffeine is metabolized in the liver by the CYP-1A2 subgroup of hepatic drug-metabolizing enzymes. Certain selective serotonin reuptake inhibitor (SSRI) antidepressants, such as fluoxetine and fluvoxamine (see Chapter 12), are potent inhibitors of CYP-1A2, and people taking these antidepressants can exhibit unexpected toxicity or intolerance to caffeine as plasma levels of caffeine rise, including de novo production of "caffeinism" (defined below), with severe anxiety reactions.

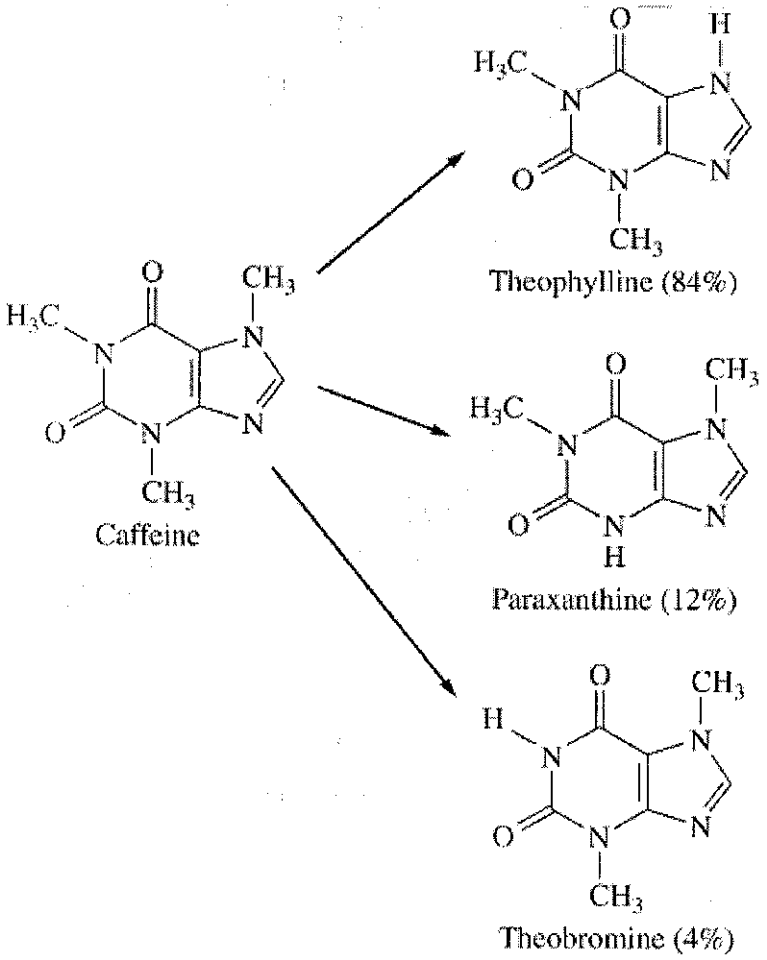

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FIGURE 6.1 Metabolism of caffeine to three end products.

Pharmacological Effects

There is a wide disparity in reactions to caffeine. Research on caffeine pharmacokinetics provides an explanation. It has been reported that the gene that controls caffeine's metabolic enzyme comes in several varieties. One version of this gene increases the rate at which caffeine is metabolized. If an individual receives a copy of this variant from both parents, that person will break down caffeine four times faster than someone who received a slow gene variant from at least one parent. The former group is termed "rapid caffeine metabolizers" and the latter group is termed "slow caffeine metabolizers." Cornelis and colleagues (2006) set out to determine the consequences of inheriting these gene variants for the risk of having a heart attack. They analyzed data from 4000 adults, half of whom had a prior heart attack. When the data from all the participants were combined, drinking 4 or more cups of coffee a day increased the risk of a heart attack by 36 percent. If the data for the slow metabolizers were removed and only the data from the fast metabolizers analyzed, then the risk was not increased. In fact, fast metabolizers had a reduced risk. Interpretation of the data suggests that the longer duration of caffeine exposure in the slow metabolizers increases the risk of heart attacks, whereas the quick elimination of caffeine by fast metabolizers reduces this adverse side effect while permitting other substances to exert beneficial actions.

Palatini and colleagues (2009) found a similar result for hypertension: slow metabolism was associated with a greater likelihood of hypertension and fast metabolism with a lesser likelihood. These results may have relevance for the well-known beneficial effects of caffeine on physical performance. Specifically, the data suggest that athletes who are fast metabolizers may have an advantage in endurance sports. This speculation was supported by a study that found caffeine led to a greater improvement of 4 minutes in fast metabolizers compared to 1 minute in slow metabolizers on a stationary bike race of 40 kilometers (Womack et al., 2012). Even the pleasurable aspects of caffeine were found to be associated with gene variants; in 2015, eight different versions of the gene were discovered that increased the likelihood of consuming coffee (Coffee and Caffeine Genetics Consortium, 2015). These outcomes may hint at why some people find coffee unappealing while others depend on it to start the day.

Beneficial Effects of Caffeine

There is mounting evidence that the world's most widely used stimulant has a variety of positive effects on both mental and physiological processes. In fact, a large study found that people who drank four to five cups of coffee a day reduced their overall risk of death by 12 (in men) to 16 percent (in women) (Freedman et al., 2012). Nevertheless, there is concern in regard to the adverse effects of increasing consumption of caffeine, especially by young people using energy drinks, particularly when combined with alcohol, such as in bars (Red Bull and vodka), premixed (Four Loco), mixed individually, or drunk separately (Howland and Rohsenow, 2013).

Cardiovascular Function. In spite of the fact that caffeine consumption can transiently raise blood pressure when taken in coffee, the blood pressure elevations are small, and long-term risks may be mitigated by compensatory actions. In fact, drinking moderate amounts of coffee is linked to lower rates of pretty much all cardiovascular disease. Cardiovascular disease risk as a function of chronic long-term coffee ingestion was evaluated in a meta-analysis, which included 36 studies and a correspondingly large pool of over 1,270,000 subjects. It was found that three to five cups of coffee per day, which constituted a modest intake, was associated with the least cardiovascular risk. If five or more cups were drunk daily, the risk was the same as if no coffee was consumed (Ding et al., 2014). Moreover, in a small trial conducted in heart failure patients, 100 milligrams of caffeine ingested hourly for five hours did not induce arrhythmias, even during exercise (Zuchinali et al., 2016).

Coffee drinkers were also less likely to have calcium in their coronary arteries than nondrinkers, with the lowest levels occurring in people who drank three or four cups daily (Choi et al., 2015). There is also no evidence that frequent consumption of caffeine-containing foods, including coffee, tea, or chocolate, has any impact on premature atrial contractions (PACs) and premature ventricular contractions (PVCs) (Dixit et al., 2016; Wilson and Bloom, 2016).

While caffeine dilates coronary arteries, it exerts an opposite effect on cerebral blood vessels; it constricts these vessels, thus decreasing blood flow to the brain by about 30 percent and reducing pressure within the brain. This action can produce striking relief from headaches, especially migraines, and is the reason why it is an ingredient in some analgesics.

Gastrointestinal. Regular coffee drinking has been shown to improve glucose metabolism and insulin secretion, and significantly reduce risk for type 2 diabetes (Floegel et al., 2012; Huxley et al., 2009). A statistical correlation between high

(Arab et al., 2011; Mulley et al., 2002). A statistical correlation between high

consumption of black tea and low prevalence of type 2 diabetes across 50 countries has also been reported (Beresniak et al., 2012). Preliminary data also showed that overweight patients treated with unroasted coffee beans in supplement form lost an average of 17 pounds over 22 weeks. The authors speculated that the weight loss may be due in part to coffee containing chlorogenic acid, a plant compound with antioxidant properties thought to reduce glucose absorption (Vinson et al., 2012). Compared with people who drank no coffee, those who drank three cups a day, whether decaffeinated or not, were about 25 percent less likely to have abnormal liver enzyme levels (Xiao et al., 2014).

Cancer. Evidence suggests that moderate-to-heavy coffee consumption (three to six cups a day across studies) can reduce the risk for numerous cancers, including endometrial (Je et al., 2011), prostate (Wilson et al., 2011), head and neck (Galeone et al., 2010), basal cell carcinoma (Song et al., 2012), colon (Schmit et al., 2016), and estrogen receptor-negative breast cancer (Li et al., 2011). These protective effects are believed to be at least partially due to coffee's antioxidant and antimutagenic properties (Je et al., 2011; Turati et al., 2011). Other reported benefits include protection against liver diseases (Molloy et al., 2012), decreased risk for gout (Park et al., 2016; Zhang et al., 2016), and a possible antimicrobial effect (Matheson et al., 2011).

Neurological. Numerous studies, including six large prospective studies, have supported a protective effect of caffeine against Parkinson's disease in both men and women (James et al., 2011; Liu et al., 2012). It does not matter if the caffeine is in coffee or tea (but decaffeinated coffee is not effective). Caffeine intake significantly reduces the risk of Parkinson's disease much more in those with high genetic susceptibility compared to those with low genetic susceptibility (Kumar et al., 2015). Furthermore, no study has ever found that coffee increases the risk of Parkinson's disease.

Patients with the highest levels of coffee consumption, four to six cups per day, had significantly lower risks of developing multiple sclerosis (MS) (33 percent reduction compared with those who drank no coffee) over various time periods (according to an early release abstract from the 2015 American Academy of Neurology meeting). Lower odds of MS with increasing consumption of coffee were observed, regardless of whether coffee consumption occurred at disease onset or 5 or 10 years prior to disease onset (Hedström et al., 2016).

Cognition and Mental Health. Numerous epidemiological studies indicate that the risk of developing Alzheimer's disease is reduced by a lifetime of consistent consumption of coffee, and that three to five cups a day are optimum for producing the protective effect (Arab et al., 2013; Cao et al., 2012). The protective effect is thought to be due to coffee's polyphenols as well as caffeine. Both of these substances are anti-inflammatory and preserve neurons associated with memory (Vassallo et al., 2014). The development of neurofibrillary tangles and amyloid plaques, which are the main Alzheimer's markers, are also thought to be prevented by caffeine (Laurent et al., 2014). Even acute administration of 200 milligrams of caffeine was found to improve memory of pictures in humans (Borota et al., 2014), while a single dose of 60 milligrams enhanced attention and alertness in adults (Wilhelmus et al., 2016). Furthermore, Sherman and colleagues (2016) reported memory improvement in college-age adults when they drank coffee in the morning, which was their nonoptimal time of day, but not in the afternoon. This was not due to an increase in physiological arousal or a general expectancy bias. In fact, because of its cognitive-enhancing possibilities, it has been argued that caffeine should be reassessed for the treatment of ADHD (Ioannidis et al., 2014). Moreover, it has been reported that honeybees given caffeine paired with sugar water were three times more likely to remember a learned floral scent after 24 hours than bees given just the sugar water. Caffeine occurs naturally in the nectar of *Coffea* and *Citrus* plant species, and it may be that the caffeine in their nectar improves the likelihood that their pollen will be distributed (Wright et al., 2013)!

Coffee consumption might also benefit mental health (Lucas et al., 2011). Women who drank two to four cups of coffee per day had a 15 to 20 percent decreased risk for depression compared with those who drank less than one cup per week. There was no association with depression and decaffeinated coffee. This is perhaps not surprising, because caffeine is a psychostimulant and is usually taken because of its activation of mood and behavior. At low doses, caffeine increases subjective arousal and physical endurance, improves concentration, elevates mood, and enhances performance on simple motor (such as driving simulation) and cognitive tasks, especially monotonous tasks (Smith et al., 2013). Fatigue is reduced and the need for sleep is delayed (Childs and deWit, 2012). Energy drinks also improve performance on laboratory tasks of memory and cognition. While this effect might be due to the fact that these drinks also contain a lot of sugar (glucose) (Ishak et al., 2012; Wesnes et al., 2016), evidence points to caffeine, rather than taurine or glucose, for reported changes in cognitive performance following consumption of energy drinks, especially in caffeine-withdrawn habitual caffeine consumers (Giles et al., 2012). In

a rare study of "real-world" conditions, it was found that long-haul truckers who reported that they used caffeinated drinks to stay awake had a 63 percent reduced likelihood of crashing compared with drivers who did not take caffeinated products (Sharwood et al., 2013).

Other Physiological Actions. Other physiological actions of caffeine include bronchial relaxation (an antiasthmatic effect), increased secretion of gastric acid (which can promote gastric reflux), and increased urine output (although this may become tolerant in habitual users).

University of Texas scientists reported that men who consumed 85 to 303 milligrams of caffeine per day (equal to the caffeine in approximately two to three cups of coffee) were up to 42 percent less likely to report the occurrence of erectile dysfunction than men who consumed less than 75 milligrams (about one cup of coffee). The results may be due to the fact that caffeine relaxes penile arteries, which causes an increase in blood flow (Lopez, et al., 2015).

Although the emphasis here has been on caffeine, similar beneficial effects have been reported for tea and cocoa. Tea may improve working memory (Schmidt et al., 2014) and may have some modest metabolic, cardiovascular, and antidiabetic benefits (Sae-tan et al., 2014). Those who drank tea were less likely to have hepatocellular carcinoma, liver steatosis, liver cirrhosis, and chronic liver disease. Laboratory tests show that chemical components of green tea inhibit cancer cell migration (Seo et al., 2016). Tea has also been associated with a lower risk of depression (Carroll, 2015).

Recent studies have reported the benefits of theobromine, which may have antitumor, anti-inflammatory, or cardiovascular potential without the undesirable side effects of caffeine. While the main mechanisms of action of theobromine, like caffeine, are inhibition of phosphodiesterases and blockade of adenosine receptors, it also has other important nonadenosinergic, antioxidant, actions (Martínez-Pinilla et al., 2015).

Adverse Effects of Caffeine

Most people adjust, or titrate, their intake of caffeine to achieve the beneficial effects while minimizing undesirable effects. Heavy consumption of coffee (12 or more cups per day or 1.5 grams of caffeine) can cause agitation, anxiety, tremors,

rapid breathing, and insomnia. The lethal dose of caffeine is about 10 grams, although ingestion in a short period of time of only 3 grams might be fatal; a blood level of 80 micrograms or more is considered potentially lethal (Sepkowitz, 2013). There are documented cases of seizures and deaths associated with caffeine consumption in energy drinks (and caffeine pills), which may be exacerbated by sleep deprivation (Ishak et al., 2012; Szpak and Allen, 2012). It has been reported that within 30 minutes of consuming an energy drink, a person's systolic blood pressure may increase by an average of 6.2 percent, compared with 3.1 percent after consuming a placebo drink. The energy drink also increased diastolic blood pressure (6.8 versus 0 percent) and serum norepinephrine levels (74 versus 31 percent) (Svatikova et al., 2015).

The FDA limits caffeine content in soft drinks, but energy drinks do not always fit into that classification and, depending on the manufacturer, may be categorized as dietary supplements, because they contain "natural" substances such as ginkgo or other herbs, which are not regulated by the FDA.

According to results of Lipshultz and colleagues (2013), energy drinks such as Red Bull are involved in more than half of the calls to poison control centers in the United States involving children less than 6 years old. Some of these children suffer from seizures and heart problems. In most of these incidents, the drinks were accidentally consumed. Nevertheless, nearly a third reported serious symptoms such as tremors, nausea, vomiting or chest pain, and erratic heart rhythms. The American Medical Association recommends limited sales to people younger than 18 (Seifert et al., 2013).

People with anxiety disorders such as panic and social anxiety disorder tend to be sensitive to the anxiogenic properties of caffeine, especially if they usually avoid caffeinated products and do not develop a tolerance to caffeine's effect, but high doses can produce anxiety even in people without such disorders. The wide variability in sensitivity to the anxiogenic effect of caffeine may be due to differences in caffeine metabolism or in the amount of adenosine receptors through which caffeine exerts its effects (discussed below) (Childs and deWit, 2012).

Caffeinism is a clinical syndrome produced by the overuse or overdoses of caffeine. Central nervous system (CNS) symptoms include increases in anxiety, agitation, and insomnia, as well as mood changes. Peripheral symptoms include tachycardia, hypertension, cardiac arrhythmias, and gastrointestinal disturbances. Caffeinism is usually dose related, with doses higher than about 500 to 1000

milligrams (1 gram, or five to ten cups of coffee) causing the most unpleasant effects. After prolonged or high doses, caffeine can produce psychosis in otherwise healthy people, especially during periods of increased stress, and worsen this condition in people with schizophrenia (Childs and deWit, 2012; Crowe et al., 2011; Persad, 2011). Cessation of caffeine ingestion resolves these symptoms.

There is also some controversy in regard to the practical benefit obtained from the use of caffeine to increase alertness. While frequent consumers may feel more alert after consumption, evidence suggests that this may be due to the reversal of acute withdrawal effects (Rodgers et al., 2010).

Perhaps the most concerning adverse effect of caffeine is its effect on sleep and the consequences of the combined use of energy drinks and alcohol on alertness and risky behavior. Although caffeine reduces fatigue and improves attention, it disturbs sleep. Even when taken during the day and certainly before bedtime, caffeine may impair the duration and quality of sleep and cause repeated awakenings (Childs and deWit, 2012; Burke et al., 2015). Compared to young adults, middle-aged adults are generally more sensitive to the effects of a high dose of caffeine on sleep quantity and quality (Robillard et al., 2015). While caffeine can reduce some of the motor impairment, sedation, and intoxication produced by alcohol (Childs and deWit, 2012), which is why it is added to alcohol, it also increases sexually risky behaviors, marijuana use, fighting, prescription drug abuse, alcohol abuse, and cigarette smoking (Ishak et al., 2012). The fact that caffeine enhances alcohol tolerance and can counteract some symptoms of a hangover may also contribute to subsequent alcohol dependence (Childs and deWit, 2012). Nevertheless, since 2010, the FDA has regarded drinks containing both caffeine and alcohol as dangerous because the caffeine masked some of the cues that people used to tell if they were intoxicated.

In 2014, almost 17 million pounds of caffeine powder was imported into the United States (Carpenter, 2015). Caffeine is commonly synthesized in pharmaceutical factories, because it is less expensive than extraction from coffee and tea plants. The majority of this large quantity of caffeine powder winds up in soft drinks, particularly in the most successful and popular brands. Regulation of caffeine differs, depending on the type of product to which it is added. Caffeine is an ingredient in dietary supplements (energy drinks), in foods and beverages, and in over-the-counter medications (NoDoz), as well as in prescription medications, particularly in drug therapy for migraine headaches.

Pure powdered caffeine—readily available from tobacco shops and the Internet for over the past decade—was packaged in the same way as protein powder and often marketed as a source of energy rather than as a stimulant. The reality is that these products are 100 percent caffeine, with a single teaspoon roughly equivalent to the amount in 25 cups of coffee. Ten grams, about a tablespoon, is a lethal dose for an adult—symptoms include rapid, erratic heartbeat, and seizures. The FDA responded to these products by posting a consumer advisory warning of the danger (Landa, 2014) and, in 2015, by sending warning letters to five producers of caffeine powder.

Did You Know?

Pure Powdered Caffeine Fatalities

Caffeine is usually thought of as a relatively safe drug with minimal risk of overdose. Unfortunately, the availability of pure powdered caffeine proves this to be an erroneous and dangerous assumption. In 2014, two young men, Logan James Stiner and James Wade Sweatt, died after ingesting too much of this stimulant. Mr. Stiner was an 18-year-old senior in high school, an athlete and prom king who was graduating in a few days. Wanting to increase his energy, he used caffeine powder that a friend had purchased through Amazon. Mr. Sweatt, 24 years old, had recently married and just graduated from the University of Alabama at Birmingham. He took the caffeine powder to avoid the sugar and sodium added to sodas and energy drinks. Each young man miscalculated the amount of the drug he took and died of an overdose. The official cause of death stated for Mr. Stiner was "cardiac arrhythmia and seizure, due to acute caffeine toxicity due to excessive caffeine ingestion." In October 2014, two U.S. senators, Sherrod Brown of Ohio and Richard Blumenthal of Connecticut, wrote to (then) FDA Commissioner Margaret Hamburg, arguing that the product should be banned by the FDA.

Mechanism of Action

Caffeine acts primarily by blocking all subtypes of adenosine receptors A_1, A_{2A}, A_3, and A_{2B}. The structure of adenosine is shown in Figure 6.2. Adenosine is a ***neuromodulator*** that influences the release of several neurotransmitters in the CNS. There do not appear to be discrete adenosinergic pathways in the CNS; rather, adenosinergic neurons form a diffuse system. Adenosine levels usually increase during the day and exert a sleep-inducing effect in the brain. By blocking adenosine receptors, caffeine promotes wakefulness; it increases respiratory and heart rates, constricts blood vessels, and releases monoamines and acetylcholine.

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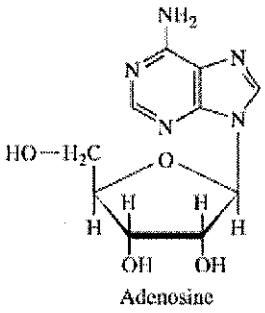

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FIGURE 6.2 Structure of adenosine. Note the similarity of adenosine to caffeine (shown in Figure 6.1).

In the striatum, type 2 adenosine receptors and type 2 dopamine receptors may combine to form a complex called a *heteromer*. When adenosine levels increase during the day, the molecules of adenosine act on this heteromer and reduce the effect of dopamine on its (associated) receptor. Caffeine blocks these adenosine receptors, which increases dopaminergic function. This may be one reason that caffeine has a beneficial effect in regard to Parkinson's disease (Bonaventura et al., 2015; Ferré et al., 2016).

Caffeine does not induce a release of dopamine in the nucleus accumbens; it leads to a release of dopamine in the prefrontal cortex, which is consistent with the drug's alerting effects and mild behavioral reinforcing properties. In addition to the direct effects of caffeine on adenosine receptors, paraxanthine, the primary metabolite of caffeine in humans, increases locomotor activity as well as extracellular levels of dopamine through a phosphodiesterase inhibitory mechanism (Ribeiro and Sebastião, 2010).

Reproductive Effects

Caffeine is consumed by at least 75 percent of pregnant women, but whether it is safe to ingest during pregnancy is an unresolved issue. As early as 1980, the FDA cautioned pregnant women to minimize their intake of caffeine. Recent reports have explored the connection between caffeine intake and rates of miscarriage (Pollack et al., 2010), fetal growth restriction (CARE Study Group, 2008), birth weight, and length of gestation (Jahanfar and Sharifah, 2009). In general, while data

epidemiological study found caffeine intake (200 to 300 milligrams per day) was consistently associated with decreased birth weight and increased odds of being small for gestational weight (Sengpiel et al., 2013). Caffeine itself does not appear to be a human teratogen, nor does it appear to affect the course of normal labor and delivery (Brent et al., 2011). One recent study, however, found that the adult offspring of mice that had been treated with caffeine while pregnant did have some neurological abnormalities, cognitive deficits, and increased susceptibility to seizures (Silva et al., 2013). Current U.S. recommendations generally advise that pregnant women limit daily intake to about 200 milligrams or less (300 milligrams per day per the World Health Organization).

Tolerance and Dependence

Chronic use of caffeine, even in regular daily doses as low as 100 milligrams, is associated with habituation and tolerance, and discontinuation may produce low-grade withdrawal symptoms. Because tolerance and dependence can occur rapidly, even after low doses, most habitual users are probably physically dependent to some degree. Individuals may become tolerant to several actions of caffeine, including diuresis, blood pressure increases, sleep disturbance, and other physiological responses, as well as subjective sensations. Tolerance is more likely with high doses of 750 to 1200 milligrams, while low doses may not produce complete tolerance (Meredith et al., 2013).

People who drink a great deal of coffee complain of headache (the most common symptom), drowsiness, fatigue, and a generally negative mood state on withdrawal. Impaired intellectual and motor performance, difficulty with concentration, and drug (caffeine) craving are also reported. Withdrawal symptoms typically begin slowly, maximize after one or two days, and cease within a few days; readministration of caffeine rapidly relieves withdrawal symptoms.

Caffeine use disorder is recognized as a diagnosable condition in the DSM-5 and three of the most significant indices from the nine criteria must be present for this diagnosis: (1) chronic craving or an inability to decrease or eliminate caffeine consumption; (2) maintained use, even after recognizing that caffeine has caused or worsened some type of mental or physical problem; and (3) elicitation of

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withdrawal symptoms or the prevention of withdrawal by continued consumption (Meredith et al., 2013).

NICOTINE

Epidemiology and Public Policy

Nicotine is one of the three most widely used psychoactive drugs in our society, along with caffeine and ethyl alcohol. Despite the fact that it has no current therapeutic applications in medicine, nicotine's widespread use and its well-established toxicity give it immense importance. Tobacco use continues to be the leading cause of preventable death and disease in the United States with about 45 million smokers, more than 400,000 premature deaths, and 300 billion dollars in health care expenses and lost productivity (Mohamed et al., 2015).

After stalling for several years, smoking rates started to fall after 2009 when, among many other tobacco-control interventions, the federal cigarette tax was increased, followed by the 2012 launch of the first federally funded mass media campaign aimed at reducing tobacco use (see Fiore, 2016 for a discussion). Smoking rates among adults in the United States fell to record lows in 2015, dropping to 15.1 from 16.8 percent in 2014, according to the Centers for Disease Control and Prevention in an early release of data from the National Health Interview Survey, 2015. Nevertheless, one in four adults still uses tobacco products at least occasionally, the CDC reported, and the use of tobacco products by youth, particularly snus, hookahs, and e-cigarettes, continues to increase.

The Family Smoking and Prevention and Tobacco Control Act became law in June 2009 and gave the FDA authority to regulate the manufacture, distribution, and marketing of cigarettes and several other tobacco products. However, this initial order did not include e-cigarettes, cigars, hookahs, pipe tobacco, or nicotine gels and dissolvables; these were added on August 8, 2016. Health warnings were also added to several tobacco products and free samples were banned. Products that entered the market after February 15, 2007, must be authorized by the FDA before they can be sold. Furthermore, tobacco products cannot be sold to individuals younger than 18 and require a photo ID to verify age. Vending machine sales of tobacco are only permitted in adult facilities. The law also provided support for additional tobacco control regulations by the FDA in the future.

This is just one of several significant developments regarding tobacco control. Another is Tobacco 21, a national campaign aimed at raising the tobacco and nicotine sales age in the United States to 21, produced and funded by the *Preventing Tobacco Addiction Foundation*, a public health nonprofit organization established in 1996. In September 2015, in a national initiative, the first federal Tobacco 21 legislation was introduced (Tobacco to 21 Act, S. 2100). Although in 2013 only 8 U.S. localities had adopted Tobacco 21 laws, by March 2016 at least 125 localities and the states of Hawaii and California had followed suit (Morain et al., 2016).

A no-tobacco-sale order (NTSO) is an order prohibiting the sale of tobacco products at a retail outlet, either indefinitely or for a specified time period (U.S. Food and Drug Administration, Center for Tobacco Products, 2016). The law states that this prohibition can be applied to a retailer who has violated tobacco restrictions five or more times over 36 months of compliance inspections. The FDA filed NTSO restrictions for the first time in October 2015 against several stores after numerous violations regarding the sale and distribution of tobacco products, including sales to minors.

The importance of smoking prevention in youth was reinforced by several reports concerning the long-term consequences of early onset smoking. Not surprisingly, high rates of smoking initiation during adolescence were not only associated with high lung cancer mortality decades later, but at a younger age than would normally be expected (Funatogawa et al., 2012; Whitley et al., 2012). Aside from the physiological costs, there are social costs for smoking. In March 2013, the University of Pennsylvania announced that beginning in July, it would no longer hire tobacco users to work in its health care system; this was accompanied by two articles that presented opposing views about the ethics of denying employment to people who smoke (Asch et al., 2013; Schmidt et al., 2013). In fact, unemployed smokers have a harder time finding work than job seekers who do not smoke, and researchers reported that smokers earn less than nonsmokers when they do become employed (Prochaska et al., 2016).

While nearly 70 percent of adults who smoke report wanting to quit and more than 50 percent reported making an attempt to stop in the year before they were questioned, only a little over 6 percent were successful (Malarcher et al., 2011). For those who succeed, however, the benefits of quitting can be dramatic. Life expectancy can increase on average from 10 to 4 years in those who quit between 25 and 64 years of age, respectively (Schroeder, 2013). Moreover, the cardiovascular

benefits of quitting are not reduced even if those who quit subsequently gained weight (at least, if they did not have diabetes) (Clair et al., 2013).

Pharmacokinetics

Although more than 4000 compounds are released by burning cigarette tobacco, nicotine is the primary addictive substance and is responsible for tobacco dependence. The other compounds produce the adverse long-term cardiovascular, pulmonary, and carcinogenic effects of cigarettes.

Nicotine is readily absorbed from every site on or in the body, including the lungs, buccal and nasal mucosa, skin, and gastrointestinal tract. Easy and complete absorption promotes the recreational abuse of smoked or chewed tobacco as well as its therapeutic use in treating nicotine dependency in chewing gums, nasal sprays, transdermal skin patches, and smokeless inhalers.

Nicotine is suspended in cigarette smoke in the form of minute particles (tars) and is quickly absorbed into the bloodstream from the lungs when the smoke is inhaled, although absorption is much slower than once thought and arterial concentrations of nicotine rise rather slowly. It is likely that blood rapidly saturates with nicotine and blood leaving the lungs (to the left side of the heart) can carry only a modest amount of drug. Thus, the arterial concentration rises slowly, even though blood carried to the brain at the initiation of smoking is nearly saturated with nicotine, accounting for the early "rush" perceived with the first cigarette.

The average cigarette contains about 8 to 10 milligrams of nicotine, but only about 20 to 25 percent of that amount enters the bloodstream. Because a cigarette is typically smoked in 10 puffs and within 5 minutes, the average smoker will absorb 1 to 2 milligrams of nicotine, but absorption can range from 0.5 to 3 milligrams. In a typical day, the average smoker absorbs anywhere from 20 to 40 milligrams.

The lethal dose for the average adult has typically been reported as 60 milligrams, but more recently suggested to be between 500 and 1000 milligrams of ingested nicotine. A smoker can readily avoid acute toxicity because inhalation as a route of administration offers exceptional controllability of the dose. By controlling the frequency of breaths, the depth of inhalation, the time the smoke is held in the lungs, and the total number of cigarettes smoked, the smoker regulates the rate of

drug intake and controls the blood level of nicotine. (People who harvest or cultivate tobacco may experience green tobacco sickness, a type of nicotine poisoning caused by dermal exposure to wet tobacco leaves).

Characteristically, smokers wake in the morning in a state of nicotine deficiency, smoke one or more cigarettes fairly rapidly to achieve a blood level of about 15 milligrams per liter, and continue smoking through the day to maintain this level. The elimination half-life of nicotine in a chronic smoker is about two hours, necessitating frequent administration of the drug to avoid withdrawal symptoms or drug craving. When nicotine is administered in the form of snuff, chewing tobacco, or gum, blood levels of nicotine are comparable to the levels achieved by smoking.

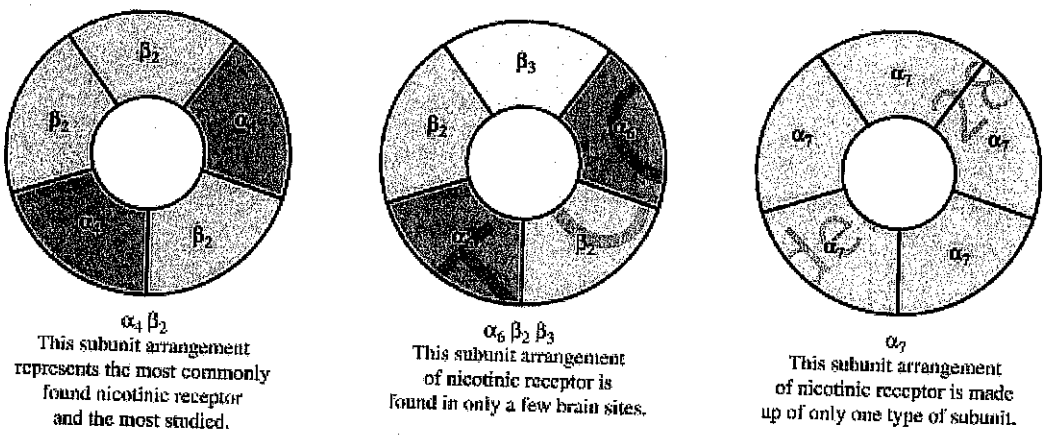
The liver metabolizes approximately 80 to 90 percent of the nicotine, primarily by the CYP-2A6 enzyme. People in whom the CYP-2A6 enzyme is absent (or inhibited by certain drugs) have higher blood levels of nicotine and lower levels of its metabolite. The constituents of tobacco smoke, however, also induce hepatic enzymes CYP1A1, 1A2, and possibly 2E1, which are involved in the metabolism of many hormones and drugs, such as caffeine, estrogen, some antidepressants, and other psychotropic agents (Fankhauser, 2013). As a result, smoking may reduce levels of these medications and smoking cessation may increase blood levels, especially in moderate or heavy smokers (10 or more cigarettes a day).

The primary metabolite of nicotine is *cotinine*, which serves as a marker of both tobacco use and exposure to environmental smoke, and is often used to measure tobacco consumption in laboratory experiments. There is some evidence that although cotinine itself is nonaddictive and has no cardiovascular effects in humans, it might have some anxiolytic and cognitive benefits (Moran, 2012).

Mechanism of Action

Nicotine exerts virtually all its CNS and peripheral effects by activating specific acetylcholine receptors (nicotinic receptors; nAChRs). These are divided into two groups: muscle receptors, found on skeletal (voluntary) muscles, and neuronal receptors, located throughout the peripheral and central nervous systems. Neuronal nicotinic receptors are composed of five subunits arranged around a central pore (which is termed a pentameric arrangement), like segments of an orange (see Chapter 3). A dozen proteins, labeled α_{2-10} and β_{2-4}, serve as subunits in

nACh receptors. The most abundant and widely distributed nACh subunit proteins in the brain are the α_4 and β_2 subunits. Animal and human imaging studies have shown that nACh receptors consisting of two α_4 and three β_2 subunits are critical for the rewarding effects of nicotine (Figure 6.3). Because nicotine stimulates these receptors, it is classified as an agonist. But while stimulation occurs at low doses, nicotine at high doses can block the receptors and thus has a biphasic action. In addition, within the time it takes to finish smoking a single cigarette, these nicotinic receptors become desensitized; that is, they temporarily do not respond to nicotine or acetylcholine. During the day, tolerance develops as nicotine builds up in the smoker's body, but this is lost overnight when the user is not smoking, which contributes to the powerful effect of the first cigarette of the day.



$\alpha_4\,\beta_2$
This subunit arrangement represents the most commonly found nicotinic receptor and the most studied.

$\alpha_6\,\beta_2\,\beta_3$
This subunit arrangement of nicotinic receptor is found in only a few brain sites.

α_7
This subunit arrangement of nicotinic receptor is made up of only one type of subunit.

Advokat/Comaty/Julien, *Julien's Primer of Drug Action*, 14e, © 2019 Worth Publishers

FIGURE 6.3 Diagram of the most common subtypes of the receptor for acetylcholine.

Menthol. Widely used as a flavoring in many products, menthol has been an additive to tobacco cigarettes since 1926. Although the concentration of menthol in cigarettes varies by brand, it is present in 90 percent of all tobacco products and used to mask the harshness of inhaled smoke, make smoking easier, and provide an oral sensation that appeals to many smokers. But smokers of menthol cigarettes are less likely to quit and have higher relapse rates than smokers of nonmenthol cigarettes. Recent studies may shed some light on the reason for this difference.

Chronic, long-term smokers of both menthol and unflavored cigarettes acquire more receptors for nicotine, particularly in neurons involved in the pathways for reward and motivation. But smokers of menthol cigarettes develop even more of these receptors (9 to 28 percent more) than smokers of unflavored cigarettes. In fact, even without nicotine, menthol increased the number of brain nicotinic

receptors, especially in the ventral tegmental area, which is part of the dopamine signaling pathway that mediates addiction. Studies show that menthol directly reduces the activation of the nACh receptor by nicotine; that is, menthol decreases the ability of nicotine to activate the nACh receptor (it is an allosteric modulator of the nACh). Nicotine does not activate the receptor channel to the same extent when coapplied with menthol (Henderson et al., 2016; Kabbani, 2013; Wickham, 2015). Beginning in 2022, the European Union will ban menthol-flavored cigarettes and the U.S. Food and Drug Administration is considering taking similar measures. In June 2017, the San Francisco board of supervisors voted unanimously to ban menthol-flavored cigarettes and flavored tobacco products, effective April 2018.

Pharmacological Effects

Effects on the Brain

In the CNS, nAChRs are widely distributed and may be located on the presynaptic nerve terminals of dopamine-, acetylcholine-, and glutamate-secreting neurons, where their activation either directly or indirectly facilitates the release of these and other transmitters, such as serotonin. Moderate smoking does not alter dopamine synthesis in the striatum (Bloomfield et al., 2014). Instead, the rewarding effect of the drug is believed to be due to the fact that nicotine increases dopamine levels in the mesocorticolimbic reward system involving the ventral tegmentum, nucleus accumbens, and forebrain (see Chapters 2 and 4). This may occur in three ways. First, nicotinic receptors on the VTA dopamine neurons directly cause dopamine release from these neurons onto the nucleus accumbens. Second, nicotine causes glutamate to be released onto VTA neurons from glutamate neurons originating in the frontal cortex (see Chapter 4). Glutamate then stimulates the VTA neurons to release dopamine. Third, nicotine desensitizes nicotinic receptors that are on GABA neurons in the VTA. These receptors are normally stimulated by Ach to release GABA onto VTA dopamine neurons, and GABA normally inhibits dopamine release. When nicotine desensitizes the nAChRs, less GABA is released; the VTA is less inhibited and releases more dopamine. Moreover, it has been reported that in laboratory animals, repeated periods of exposure to and subsequent withdrawal from nicotine increased its rewarding value and also upregulated nicotinic brain receptors. It was speculated that this phenomenon might be one reason why smokers relapse frequently (Hilario et al., 2012). Morel and colleagues (2014)

smokers relapse frequently (Hajek et al., 2012). Morel and colleagues (2014)

identified a specific alpha subunit of the nicotinic receptor that is an important regulator of nicotinic-induced dopamine activation and the genetic component that controls the expression of that subunit. This links genetics to receptor structure and to self-administration of nicotine.

Studies in humans found that the motivation to smoke (puff rate) predicted the magnitude of dopamine release in the limbic striatum and the amount of dopamine release was correlated with decreased craving and withdrawal symptoms. Results also support the preferential involvement of the limbic striatum in the motivation to smoke, anticipation of pleasure from cigarettes, and relief of withdrawal symptoms (Le Foll et al., 2014). Volume, surface area, and shape of the striatum were also related to measures of craving (Janes et al., 2015). The first demonstration of tobacco smoking-induced *cortical* dopamine release in humans was shown by Wing and colleagues (2015). Studies in the mouse found that under certain conditions, such as simultaneous intake of the two drugs, prior nicotine use promoted ***cocaine*** self-administration. This result suggests how nicotine in products such as e-cigarettes may be a "gateway" to other drug use (Kandel and Kandel, 2014).

Nicotine-induced release of acetylcholine may improve cognitive performance and may also be responsible for the arousal effects commonly seen with smoking. Very few studies, however, have looked at nicotine's effect on memory performance in normal *nonsmokers*. There is some evidence for the improvement of working memory in nonsmokers, but only under specific experimental conditions; one study did find that nicotine patches improved some aspects of attention in nonsmokers who had no preexisting cognitive impairments (Levin et al., 2006). Such outcomes have raised interest in the development of nicotinic drugs as "cognitive enhancers," which might be beneficial in treating Alzheimer's disease. There is stronger evidence suggesting a protective role for nicotine receptors in Parkinson's disease; as with caffeine, tobacco smoking is associated with a reduced likelihood of Parkinson's disease (Quik et al., 2012). The potential benefits of nicotine, its metabolites, and related compounds for treating Parkinson's disease are discussed by Barreto and colleagues (2015). High doses have toxic effects, but low doses may be therapeutic.

Smoking and Mental Health. In the United States, individuals with mental disorders account for 40 to 50 percent of all cigarettes consumed (Smith et al., 2014). Unlike in those not mentally ill, smoking rates have changed little in the mentally ill (Cook et al., 2014). In fact, associations of smoking with drug and alcohol abuse, attention

al., 2014). In fact, associations of smoking with drug and alcohol abuse, attention deficit/hyperactivity disorder, bipolar disorder, and antisocial personality disorder have each increased over the last decades (Talati et al., 2016). Moreover, tobacco smoking is an independent risk factor for developing schizophrenia and nonaffective psychoses with a dose-response association, although the risk is much lower for bipolar disorder (Kendler et al., 2015). Patients with schizophrenia, bipolar disorder, or depression also have a significantly increased risk of tobacco-related mortality (Callaghan et al., 2014) and of being diagnosed with nicotine withdrawal syndrome (Smith et al., 2014). Conversely, smokers reported more frequent symptoms compared with nonsmokers of depressed mood, poor sleep, low energy, hopelessness, lack of appetite, lack of interest, and trouble concentrating (Parikh et al., 2014). Smoking is also associated with an increased risk of panic attacks and quitting smoking helps to reduce such attacks (Bakhshaie et al., 2016).

The good news is that smoking cessation treatment can be effective in people with mental illness, even with comorbid substance abuse, and can improve the psychiatric condition (Cook et al., 2014; Taylor et al., 2014). Adding smoking cessation treatment to the treatment for illicit stimulant use did not worsen the latter and even enhanced abstinence from non-nicotine use as well as from nicotine use (Winhusen et al., 2014). However, patients with a history of substance abuse and who take antidepressants may have a lower smoking cessation rate than those without such a background (Zorick et al., 2014). Smoking cessation itself in people with no psychiatric disorders did not worsen mental health (Taylor et al., 2015).

Acute Effects on the Body

In the peripheral nervous system, nicotine causes an increase in blood pressure, heart rate, cardiac contractility, release of epinephrine (adrenaline) from the adrenal glands, and an increase in the activity of the gastrointestinal tract.

In nonatherosclerotic coronary arteries, nicotine produces vasodilation, increasing blood flow to meet the increased oxygen demand of the heart muscle. In atherosclerotic coronary arteries (which cannot dilate), however, cardiac ischemia can result when the oxygen supply fails to meet the oxygen demand created by the drug's cardiac stimulation. This occurrence can precipitate angina or myocardial infarction (heart attack).

In the early stages of smoking, nicotine causes nausea and vomiting by

stimulating both the vomiting center in the brain stem and the sensory receptors in the stomach. Tolerance to this effect develops rapidly. Nicotine also reduces weight gain, probably by reducing appetite and altering taste bud sensitivity. Stomach secretions are inhibited, but bowel activity is stimulated; in people with little tobacco tolerance, the drug is a laxative. Nicotine stimulates the hypothalamus to release antidiuretic hormone, which causes fluid retention. The activity of afferent nerve fibers coming from the muscles is reduced by nicotine, leading to a decrease in muscle tone. This action may be involved (at least partially) in the relaxation a person may experience as a result of smoking.

Tolerance and Dependence

While some of the acute effects wane, there is little tolerance to the primary rewarding effects of nicotine. On the other hand, nicotine clearly induces both physiological and psychological dependence in a majority of smokers. As early as 1988, the surgeon general of the United States (U.S. Department of Health and Human Services, 1988) concluded that tobacco use is addictive, nicotine was the substance in tobacco that causes addiction, and nicotine addiction was pharmacologically as powerful as addiction to other drugs, such as heroin and cocaine.

A well-defined withdrawal syndrome has been delineated, which is alleviated by nicotine replacement. Abstinence symptoms include a severe craving for nicotine, irritability, anxiety, anger, difficulty in concentrating, restlessness, impatience, increased appetite, weight gain, and insomnia. Symptoms usually begin within about two hours after the last use of tobacco, peak within 24 to 48 hours, and gradually decline over the next 10 days to several weeks. Mild depression (dysphoria and anhedonia) and increased appetite may persist for months. In one study, smoking cessation produced a mean increase in body weight of 4 to 5 kilograms after 12 months of abstinence, although most weight was gained in the first 3 months (Aubin et al., 2012). The difficulty in handling cigarette dependence is illustrated by the fact that cigarette smokers who seek treatment for other drug and alcohol problems often find it harder to quit cigarette smoking than to give up the other drugs. Even Sigmund Freud continued his cigar habit (20 per day) until death, in spite of an endless series of operations for mouth and jaw cancer (his jaw was eventually totally removed), persistent heart problems that were exacerbated by smoking, and numerous attempts at quitting.

Unlike other drugs that produce physical dependence, the severity of tobacco withdrawal does not seem to be related to the dose (heavy or light amount of smoking), the duration of the habit, previous attempts at quitting, sex, age, education, or alcohol and caffeine use (McKim and Hancock, 2013). On the other hand, there is some evidence that genetic factors play a role in the development of dependence, specifically the probability of smoking 20 or more cigarettes daily, earlier and faster onset of heavy smoking, and the likelihood of relapse after quitting (Belsky et al., 2013).

Toxicity

Central Nervous System

Studies of the effects of nicotine on brain anatomy report a loss of brain matter in the cerebral hemispheres in current smokers (Fritz et al., 2014; Morales et al., 2014), as well as differences between smokers and nonsmokers in the strength of some connections between various brain structures (Addicott et al., 2015; Lerman et al., 2014). Evidence suggests that enzyme activity in the brain (as opposed to the liver) could affect brain nicotine levels and influence smoking behavior (Garcia et al., 2015). Another study also revealed the deleterious effect of smoking on the CNS in multiple sclerosis (MS); patients who continued to smoke experienced a faster onset of secondary progressive MS (SPMS) (Hillert et al., 2015).

Cardiovascular Disease

The carbon monoxide in smoke decreases the amount of oxygen delivered to the heart muscle, while nicotine increases the amount of work the heart must do (by increasing the heart rate and blood pressure). Both carbon monoxide and nicotine increase the incidence of atherosclerosis (narrowing) and thrombosis (clotting) in the coronary arteries. These three actions (among others) seem to underlie the dramatic increase in the risk of death from coronary heart disease in smokers compared to nonsmokers (Teo et al., 2006). Cigarette smokers manifest a 50 percent increase in the progression of atherosclerosis when compared with people who have never smoked.

Besides the coronary arteries, atherosclerosis occurs in other arteries as well, most notably the aorta (in the abdomen), the carotid arteries (in the neck), and the femoral and other arteries of the legs. Cigarette-induced occlusion of these vessels blocks the blood flow to important body organs and results in ischemic damage, strokes, and other disorders. However, in women who quit smoking for 20 years or more, this risk dropped to the level of those who never smoked compared to current smokers (Sandhu et al., 2012).

Pulmonary Disease

When tobacco smoke is inhaled, tar and ash are deposited on the moist membranes through which oxygen and carbon dioxide have to cross to and from the blood. Eventually, these toxins overcome the processes by which pollutants are removed and destroyed in the lung. This leaves the lung more susceptible to infections and other toxic damage. Chronic smoking results in difficulty in breathing, wheezing, chest pain, lung congestion, emphysema (a form of irreversible lung damage), and increased susceptibility to infections of the respiratory tract.

Cancer

Although nicotine itself is not carcinogenic, the relationship between smoking and cancer is now beyond question. A new study (Lortet-Tieulent et al., 2016) has found that 28.6 percent of all cancer deaths in the United States are attributable to cigarette smoking: 22.9 percent of cancer deaths in women and 33.7 in men. This is likely an underestimate because the study only included data on cigarettes and not cancers caused by secondhand smoke, pipes, hookahs, cigars, smokeless tobacco, and electronic nicotine delivery systems or deaths from many other diseases linked to smoking.

Cigarette smoke contains diverse carcinogens and cigarette smoking is the major cause of lung cancer in both men and women. Smoking is also a major cause of cancers of the mouth, voice box (larynx), and throat. Concomitant alcohol ingestion greatly increases the incidence of these problems. In addition, cigarette smoking is a primary cause of bladder cancer and pancreatic cancer, and it increases the risk of cancer of the uterine cervix twofold.

It has several effects on the visual system: it increases the risk of cataract formation and Graves' ophthalmopathy, an autoimmune disease associated with too much thyroid activation, in which the eyes bulge because of swelling and inflammation (Kapoor and Jones, 2005). Smoking also causes premature aging of the skin (at least partly because of blood vessel constriction) and current smokers have a greater risk of developing cutaneous squamous cell cancer compared to nonsmokers (Leonardi-Bee et al., 2012).

Smoking even increases, by 17 percent, death from diseases that do not have established relationships with cigarette smoking (Carter et al., 2015).

The FDA has established a list of 93 harmful and potentially harmful constituents (HPHCs) that tobacco companies will eventually be required to report for every regulated tobacco product sold in the United States. All HPHCs included on the list cause or may cause serious health problems, including cancer, lung disease, and addiction to tobacco products. The complete list includes ammonia, formaldehyde, nicotine, nitrosamines, carbon monoxide, and other toxins.

Effects of Passive Smoke

Many nonsmokers are exposed to the toxic agents in the passive smoke exuded by burning and exhaled cigarettes, pipes, cigars, and like tobacco products, called *environmental tobacco smoke, secondhand smoke, or passive smoking*. In 1993, the Environmental Protection Agency classified secondhand smoke as a Class A carcinogen. In 2011, the first global assessment published data from 2004 across 192 countries and concluded that secondhand smoke accounted for about 1 percent, or about 603,000 deaths, worldwide (Öberg et al., 2011). Of particular concern, 165,000 children were estimated to have died from smoke-related respiratory infections, mostly in Southeast Asia and Africa. Children whose parents smoke have a higher risk of sudden infant death syndrome, ear infections, pneumonia, bronchitis, and asthma. Data from the National Health and Nutrition Examination Surveys from 2003 through 2010 of children ages 6 to 19 who had been diagnosed with asthma showed that 53 percent had cotinine in their blood. Smoke exposure increased doctor visits, disturbed sleep, and impaired physical activity (Akinbami et al., 2012). Prenatal exposure has also been found to increase subsequent psychiatric problems in offspring of smokers (Ekblad et al., 2010). There is even evidence that children who are exposed to secondhand smoke are more likely to start smoking themselves

than children who are not exposed to passive smoke (Doweiko, 2012). Worldwide, 40 percent of children are regularly exposed to secondhand smoke and children account for more than a quarter of all deaths and over half of all healthy years of life lost due to exposure to secondhand smoke. Legislation to reduce the effects of secondhand smoke through public smoking bans have led to drops in both preterm births and childhood asthma hospitalizations (Been et al., 2014; Kalkhoran and Glantz, 2014).

Effects During Pregnancy

Cigarette smoking reduces oxygen delivery to the developing fetus, causing a variable degree of fetal hypoxia. This condition may underlie the reported increases in irritability and increased muscle tone in the neonate (Stroud et al., 2009) and even longer-term intellectual and physical deficiencies (Abbott and Winzer-Serhan, 2012). Furthermore, cigarette smoking produces a two- to threefold increase in being small for gestational age (SGA) or being born preterm (McCowan et al., 2009). Even women exposed to passive smoke inhalation have low-birth-weight children. In fact, when a smoking ban was introduced in northern Belgium, gradually over successive years (2006, 2007, and 2010), there was a statistical decrease in the rate of preterm births. The rate dropped the most during the last phases, when smoking was banned in restaurants and in bars selling food (Cox et al., 2013). These risks can be reversed if smoking is stopped early in pregnancy. Also, the weight of a smoker's small for gestational age offspring usually becomes normal at about 18 months of age.

Programs designed to reduce smoking behaviors and nicotine dependence during pregnancy offer special challenges because the safety of pharmacological interventions (bupropion, nicotine replacement therapies, varenicline) has not been established. Nevertheless, in a French study involving 402 pregnant women (all over 18 years old and between 12 and 20 weeks pregnant) who smoked at least five cigarettes a day, the effectiveness of 16-hour nicotine patches was evaluated. In addition to receiving behavioral support for smoking cessation, participants were randomly chosen to receive either nicotine or placebo patches throughout their pregnancy. Researchers measured birth weight and total abstinence (as confirmed by carbon monoxide levels in exhaled air from the pregnant women). Neither birth weight nor smoking cessation showed any improvement with nicotine patches compared with placebo patches. Only 11 women (5.5 percent) given the nicotine

patch achieved complete abstinence, which was comparable to the 10 women (5.1 percent) who received the placebo patch (Berlin et al., 2014).

Pharmacological Approaches to Nicotine Dependence

As nicotine dependence gradually became recognized during the 1990s, a variety of pharmacological treatments were developed to "reduce the harm" of smoking, with the presumed goal of promoting cessation. These are sometimes referred to as *potentially reduced exposure products* (PREPs), developed as a means of tobacco harm reduction (THR).

According to the U.S. Public Health Service (2008) and the U.S. Preventive Services Task Force (Patnode et al., 2015), several products are considered to be first-line options for smoking cessation, also called *nicotine replacement therapy* (NRT). These include nicotine gum, lozenges, inhalers, mouth spray, nasal spray, the transdermal nicotine patch, orally dissolvable films, and low-nicotine cigarettes (Hansson et al., 2012). Dissolvable tobacco consists of fine-grained tobacco formed into pellets, strips, or toothpick-size "sticks" that dissolve in the mouth. Nontobacco, or non-NRT agents, include the antidepressant bupropion and the partial nicotine agonist varenicline (Chantix). The efficacy of other smoking cessation medications is less well established (Siu et al., 2015).[2]

Several other forms of nicotine administration have also become popular, including sublingual products, referred to as "snus,"[3] water pipes (hookahs), and electronic cigarettes.

Snus consists of moist powdered tobacco (with salt and water) sold as small mesh pouches, which are held in the mouth for about 30 minutes and then discarded. A snus user packs the tobacco into the upper lip to get the nicotine and swallows the by-product, rather than spit it out. One 2-gram portion of snus increases blood nicotine concentration to around 15 nanograms per milliliter of tobacco within 30 minutes. In contrast, a cigarette delivers about 23 nanograms per milliliter of nicotine in the first five minutes, but by 30 minutes the levels of nicotine in the body are comparable between the two. The products are promoted as a way to get a nicotine fix when you cannot smoke, like nicotine gum. Except for Sweden, the sale of snus has been banned throughout the European Union since 1992.

In the spring of 2015, the FDA denied a petition by two tobacco companies to ease up on the warnings around smokeless tobacco. For now, they will carry the same warning labels stating that they are "not a safe alternative to cigarettes" currently required for other smokeless tobacco products. As of November 2015, eight snus products have been the first to be cleared under the FDA's premarket tobacco application (PMTA) pathway, established after Congress authorized the agency to regulate tobacco products.

Using a *hookah* (also called a *shisa, narghile,* or *water pipe*) involves smoking substances through a water pipe such that the smoke passes through the water and is cooled before inhalation. Originating in northern Africa and southwest Asia, it is a tradition at least four centuries old and is now very popular among adult men in Middle Eastern countries (Brockman et al., 2012). Hookah smoking, however, is spreading worldwide; in the United States, adolescents and young adults are increasingly adopting this habit. Apparently, many hookah smokers believe it is less harmful and addictive than smoking cigarettes. Studies so far show that this is not the case, and that both short- and long-term effects of water-pipe tobacco smoking are just as harmful (Hakim et al., 2011). Secondhand exposure to hookah smoke is also an underappreciated health hazard for workers in the increasing number of venues that allow water pipes (Zhou et al., 2016). Smoking hookahs more than doubles the odds that a noncigarette smoker will begin smoking within two years, according to a recent study (Soneji et al., 2015). Using snus increases the risk of starting smoking by more than sixfold. At follow-up, among those who did not smoke cigarettes at baseline, 39 percent of hookah users had begun smoking, compared with 20 percent of those who had not used water pipes. Similarly, among baseline nonsmokers, 55 percent of smokeless tobacco users had begun smoking at follow-up, compared with 21 percent of those who did not use snus.

Vapor Products: E-cigarettes and Electronic Nicotine Devices

Perhaps the most controversial product in the PREP category is the *electronic cigarette*, or *e-cigarette*. Predecessors appeared as early as 1965 and 1986, but current versions were developed in 2003 by the Chinese pharmacist Hon Lik, a former deputy director of the Institute of Chinese Medicine in Liaoning Province (U.S. Department of Health and Human Services, 2016). The e-cigarette has no tobacco. Instead, users add drops of liquid nicotine to the battery-powered device, which delivers a propylene glycol–nicotine vapor that is inhaled. Laboratory studies

which delivers a propylene glycol–nicotine vapor that is inhaled. Laboratory studies suggest that e-cigarettes may be safer than tobacco products because they essentially contain fewer nonnicotinic toxic substances and they do not produce secondhand smoke. They also have the advantage of providing the behavioral stimuli that is often conditioned to smoking—the physical act of holding a cigarette and inhaling and exhaling a vapor. The presence of diethylene glycol, however, a toxic chemical found in antifreeze, raises safety concerns. Users can also modify the apparatus to produce more vapor, increase the amount of nicotine, or add other ingredients besides nicotine. The Vype eTank is a refillable e-cigarette that gives users control over the nicotine strength and flavor combinations that suit them; there are a range of Vype eLiquid flavors in a variety of nicotine strengths. There is a wide variation in the amount of nicotine, even in different samples of the same product.

Devices known as *vape-pens* are larger than typical e-cigarettes. They have bigger batteries that are capable of raising the temperature, and consequently the nicotine level, higher than the standard e-cig. These may be appealing because the blood level of nicotine is lower with e-cigs than with normal cigarettes. Unfortunately, the increased temperature also increases the level of toxins and carcinogens. Higher nicotine levels, or batteries, have also been introduced by the tobacco companies. One example is a new e-cigarette formulation that the company Njoy developed to increase lung absorption so that the nicotine level approaches 70 percent of a regular cigarette (Moyses et al., 2015).

The Voke, developed in the UK, completely does away with electronic components, batteries, and heat, relying instead on a pressurized canister containing 20 refills of pharmaceutical-grade nicotine activated by a breath-controlled microvalve. Every time the user draws on the device, they are administered a precise dose of nicotine. Basically, the Voke is an e-cigarette-shaped inhaler that does not produce any kind of visible smoke or vapor. But it does reproduce other elements of smoking, including a typical "throat catch," that is, the sensation of smoke in the back of the throat. At the beginning of 2017, this product was licensed to the company Kind Consumer, which hopes to introduce it in 2018.

Philip Morris International's newest product, the iQOS, is a hybrid between a cigarette and an e-cigarette. The Marlboro-branded iQOS uses real tobacco in the shape of small cigarettes ("heat sticks") that are inserted into the heating device and heated at high temperatures, but not actually burned. The iQOS only heats the tobacco to 350 degrees Celsius, whereas tobacco cigarettes burn at around 800 degrees, but the product delivers a mouthful of tobacco-flavored vapor without

smoke or tar. Smokers who use iQOS will still have more chemical exposure than smokers who switch to one of the vapor alternatives. As of September 2017, this product was not approved in the United States.

E-cigarettes are not devoid of toxicity. In 2014, the American Association of Poison Control Centers reported that more than 3700 children were exposed to liquid nicotine, a dramatic increase from prior years. The next year, New York fined four producers of liquid nicotine made for electronic cigarettes because the packaging was too easy for children to open, which violated a 2014 law. That same year, attorneys general of 33 states in the United States argued for health warning labels to be required by the FDA on liquids containing nicotine as well as several other tobacco items. This request resulted in a new set of labeling and advertising regulations from the FDA. Between March 2013 and March 2014, the FDA received over 50 complaints of electronic cigarette injury—about the same as the number received in all of the preceding five years. Effects included difficulty breathing, headache, cough, dizziness, sore throat, nosebleeds, chest pain, and allergic reactions. At the May 2015 annual meeting of the American Thoracic Society, Dr. P. V. Dicpinigaitis reported that exposure to electronic cigarette vapors significantly reduced the sensitivity of the cough reflex in a group of healthy volunteers. In experiments on mice, scientists found that e-cigarette vapor could harm the lungs and make them more susceptible to respiratory infections, and that e-cigarette vapors appeared to increase the aggressiveness of dangerous bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), making it more virulent (although cigarette smoke has a much greater effect) (Crotty Alexander et al., 2014). E-cigarette use is associated with higher cardiac sympathetic tone and increased oxidative stress, but it remains unclear to what extent these changes represent an increase in cardiovascular risk (Moheimani et al., 2017). Moreover, some popular e-cigarettes get so hot that they, too, can produce some of the carcinogens found in cigarettes and at similar levels.

It is generally believed that the inhaled chemicals produced from an e-cigarette are less dangerous than the nearly 300 carcinogens that are released from a regular cigarette (Shahab et al., 2017), but it is not completely clear what those chemicals are. The vaping process itself may produce a more addictive form of nicotine, called *free base*, than smoking (El-Hellani et al., 2015). The high-powered e-cigarettes, known as *tank systems*, produce formaldehyde, a known carcinogen, along with the nicotine-laced vapor. The toxin is formed when liquid nicotine and other e-cigarette ingredients are subjected to high temperatures (Jensen et al., 2015). In addition to this inherent toxicity, Krishnan-Sarin and colleagues (2017) report that many teens

this inherent toxicity, Krishnan-Sarin and colleagues (2017) report that many teens who use electronic cigarettes have tried "dripping," in which small amounts of e-liquid are dropped directly onto an e-cigarette's atomizer coil to vaporize the liquid at a high temperature; users then inhale the vapor immediately. The most commonly reported reasons for dripping included: it "produces thicker clouds of vapor," the "flavor tastes better," and it provides "a stronger throat hit." The authors noted that e-liquids exposed to high temperatures produce significant increases in the levels of formaldehyde, acetaldehyde, and acetone in the vapors. Dinakar and O'Connor (2016) provide a review of the health effects of electronic cigarettes.

E-Cigarettes and Smoking Cessation. But, the most important question is, do e-cigarettes really help smokers to stop or are they merely a steppingstone to cigarettes and other tobacco products? This issue has caused much debate among the experts. The main reason for regular e-cigarette use cited in surveys has been "to kick" the tobacco habit, and some public health experts support that "harm-reduction" strategy.

Arguments in favor of e-cigarettes are that they are safer than conventional cigarettes and have the potential to promote cessation. The amount of toxic substances is lower than that in tobacco smoke, the carcinogenic content is "negligible," the risk of nicotinic poisoning is minimal if they are used as intended, and other components of the vapor are not dangerous, at least in people without respiratory difficulties. The increase in e-cigarette use is expected to be more common among people who already smoke, and e-cigarettes might help motivated smokers quit by reducing their urge to smoke.

A panel of public health experts from the United Kingdom published a report in 2015 regarding the relative effects of electronic cigarettes. They determined that e-cigarettes were 95 percent less dangerous than regular cigarettes. In addition, they did not believe that there was sufficient evidence to argue that e-cigarette use led to subsequent use of other tobacco products (Green et al., 2016). In January 2016, UK drug regulators gave the go-ahead for a British American Tobacco (BAT) e-cigarette, the e-Voke, to be sold as a therapy for quitting smoking.

Those against e-cigarettes argue that all forms of nicotine are addictive and substantially more harmful than not smoking at all. Moreover, opponents argue that e-cigarettes or similar alternatives might be used by smokers to increase their consumption of nicotine, rather than discontinue conventional cigarettes. Regulatory authorities could make e-cigarettes safer by requiring child-proof packaging, prohibiting the addition or production of potentially dangerous

packaging, prohibiting the addition of production of potentially dangerous contaminants in products with nicotine, and by capping the voltage and temperature specifications of these devices, which would reduce formaldehyde exposure. It is generally acknowledged that while e-cigarettes are less harmful than conventional cigarettes, they are still more risky than total abstention from tobacco and could be made safer (Lindblom, 2015).

The hope that cigarette smokers would switch to e-cigarettes and benefit from lower rates of heart disease, lung disease, and cancer assumes that the only persons who use e-cigarettes would be current tobacco users looking for a safer cigarette. But there is concern that e-cigarettes serve as the entryway for young nontobacco users to become addicted to nicotine. This concern is supported by data showing that a third of e-cigarette users were nonsmokers and 1.4 percent were never smokers (Avdalovic and Murin, 2015). According to one Web-based survey, electronic cigarettes did not help smokers quit or even smoke less. Of course, these respondents were not trying to quit. On the other hand, one small placebo-controlled trial suggested that although e-cigarettes were at least as good as nicotine patches in helping smokers quit, cessation rates were low either way at 6 to 7 percent (Grana et al., 2014). In fact, the results of a subsequent study suggested that e-cigarettes are linked with *less* smoking cessation: individuals who used e-cigarettes had 28 percent lower odds of quitting cigarettes compared with those who did not use e-cigarettes. It did not even matter if smokers had an interest in quitting or not; there was no difference in e-cigarette use between the two groups (Kalkhoran and Glantz, 2016).

In the 2015 National Youth Tobacco Survey, e-cigarettes were the most commonly used tobacco product among teens for the second year in a row. According to the Surgeon General's Report, e-cigarette use among high school students increased "an astounding 900 percent" from 2011 to 2015. In 2015, nearly 38 percent of high schoolers reported having tried an e-cigarette at least once. Researchers found that 67 percent of respondents considered e-cigarettes to be "healthier" than regular cigarettes (Wills et al., 2015). The most common reasons teens gave for initially trying e-cigarettes were curiosity, a cool factor, and because of their friends. But six months later, none of those reasons were significant predictors of continued e-cigarette use. Only 5.9 percent of students said they tried e-cigarettes in an effort to quit smoking, but smoking cessation was the only reason that was significantly associated with continued e-cigarette use. The authors also noted that after 6 months, 80 percent of teens who said they were using e-cigarettes to quit smoking were still smoking traditional cigarettes (Bold et al., 2016). Adolescents who vaped

frequently, defined as weekly smoking or more than two cigarettes per day, were more likely to be more frequent and heavier smokers six months later. Vaping was not associated with smoking reductions (Leventhal et al., 2016). A 2016 analysis of teenagers in Hawaii showed e-cigarette use to be positively associated with both tobacco initiation and increased smoking frequency. E-cigarettes had no benefit in reducing tobacco use in teens who smoked (Wills et al., 2017).

Moreover, a survey of Connecticut high school students in the spring of 2014 found about 18 percent of e-cigarette users and cannabis users used e-cigarettes to vaporize cannabis (Morean et al., 2015).

Nicotine Replacement Therapies

As noted above, while most smokers say they want to quit, only a small percent are successful. Current tobacco dependence treatments have a 12-month abstinence success rate of 22 percent at best, but the relapse rate within 1 year is high and over 90 percent of over-the-counter nicotine replacement therapy (NRT) users relapse within 6 months (Mohamed et al., 2015). Whether cessation occurs by a gradual reduction in the number of cigarettes smoked or by quitting abruptly with no prior decrease, the quit rates are the same (Lindson-Hawley et al., 2012). People who used reduced-nicotine cigarettes (≤2.4 milligrams per gram of tobacco) did decrease the number of cigarettes they smoked per day compared with people who smoked their regular brand (or 15.8 milligrams per gram of tobacco) over a six-week trial, but the difference was not impressive (Donny et al., 2015). Nevertheless, the benefit might be cost effective (Fiore and Baker, 2015).

To alleviate the symptoms of nicotine withdrawal while the smoker quits the smoking habit, NRT products offer nicotine exposure in the absence of tobacco. In the United States, the patch, lozenge, and gum can be sold over the counter, while the nasal spray and oral inhaler are only available with a prescription. Some countries sell a nicotine mouth spray and sublingual tablet, but these are not available in the United States. It is important to avoid smoking while using NRTs; psychological counseling in conjunction can be useful. Smokers, however, who were sent nicotine patches in the mail were more than twice as likely as smokers who did not receive the posted patches to report that they were no longer smoking six months later, even though they received no behavioral support. This suggests that NRT alone is an effective strategy to help smokers stop smoking (Cunningham et al., 2016). Burghardt and Ellingrod (2012) describe clinical applications for the

therapeutic use of NRTs.

The second category of medications used for smoking cessation consists of drugs not considered to be NRTs, although they may act on the nicotinic receptor. Currently, these include antidepressants, primarily bupropion (Zyban), and *partial nicotine receptor agonists*, such as varenicline, dianicline, and cytosine (trade name Tabex).

In their review, Hughes and coworkers (2007) concluded that the antidepressants *bupropion* (Wellbutrin, Zyban) and *nortriptyline* (Pamelor) double a person's chances of giving up smoking and have an acceptable rate of side effects. SSRI antidepressants such as *fluoxetine* (Prozac) are not effective. Of the two, bupropion is the most studied and most widely used. Bupropion delays smoking relapse and also results in less weight gain. Interestingly, bupropion and nortriptyline appear to work equally well in both depressed and nondepressed smokers; this suggests that these drugs help smokers quit in some way other than through their action as antidepressants. Bupropion inhibits $\alpha_4\beta_2$ and α_7 nAChRs, inhibits nicotine-induced dopamine release, and reduces nicotine self-administration—pharmacological properties that may contribute to the smoking cessation effect (Slemmer et al., 2000).

Partial Nicotinic Agonists

In late 2006, a new approach to treating nicotine dependence was introduced. *Varenicline* (Chantix) (Jorenby et al., 2006) and two other drugs, cytisine (West et al., 2011) and dianicline (Tonstad et al., 2011), are pharmacologically classified as *partial nicotine receptor agonists*. By partially stimulating the receptor, they reduce withdrawal symptoms, but block access of nicotine to the receptor. Continued smoking is less satisfying and may help the person to quit and maintain abstinence. Because nicotine indirectly induces the release of dopamine (which produces its stimulant and reinforcing action), these drugs also enable a low-level release of dopamine (Zierler-Brown and Kyle, 2007). Figure 6.4 compares the effect on nicotinic receptors and dopamine release of smoking, smoking abstinence, and varenicline administration.

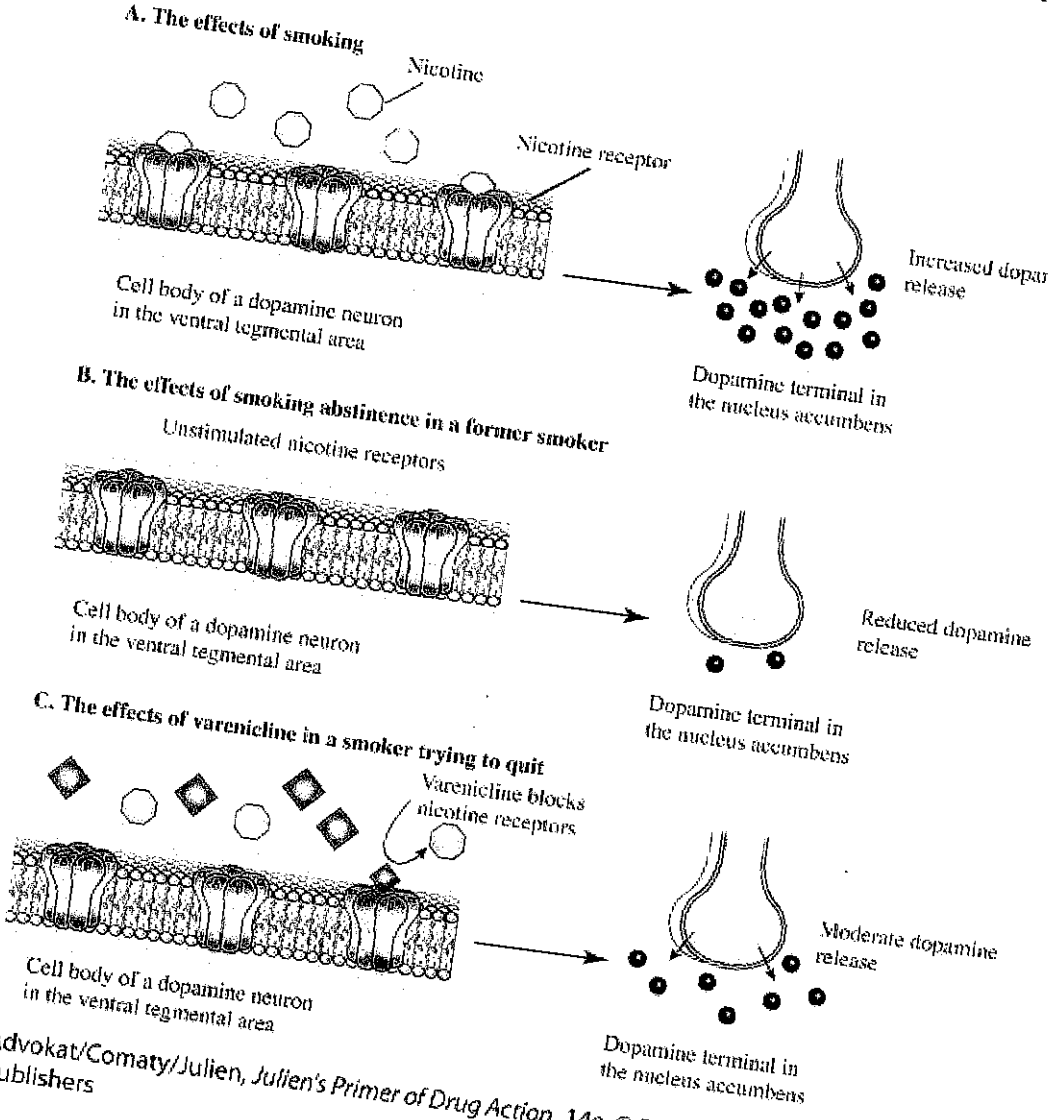


FIGURE 6.4 The effect on nicotine receptors and dopamine release of **A.** nicotine from cigarettes, **B.** nicotine withdrawal, and **C.** varenicline administration.

Although initial reports were positive, subsequent outcomes were less impressive. Dianicline was not very effective in promoting abstinence and is no longer under development. Cytisine is an unusual compound extracted from the seeds of *Cytisus laborinum* (Golden Rain acacia) (West et al., 2011). It was first marketed in Bulgaria in 1964 and has been available in former Eastern Bloc countries for over 40 years under the brand name Tabex; it is not available in the United States. Cytisine results have been very modest in achieving the cessation of nicotine addiction (Walker et al., 2014).

A long debate over Chantix and its safety began soon after its 2006 approval. Patients and their doctors started reporting suicidal thoughts, aggression, depression, and agitation. After reviewing the evidence, the FDA gave the drug a black box warning in 2009, which it updated in 2011. In 2015, the FDA added the warning that until patients knew how Chantix affected their ability to tolerate alcohol, they should decrease the amount of alcohol they drink, and that patients who had a seizure while taking Chantix should stop the medicine and seek medical attention immediately. That year, conflicting publications about the psychiatric consequences of varenicline (Molero et al., 2015; Thomas et al., 2015) prompted the FDA to recommend and help design a clinical trial called EAGLES to answer the suicidality issue not just for Chantix, but also for other smoking cessation products, namely Zyban (*bupropion*) and the nicotine patch. The review of the clinical trial results confirmed that Chantix, Zyban, and nicotine replacement patches were all more effective for helping people quit smoking than a placebo, regardless of whether or not they had a history of mental illness (Anthenelli et al., 2016). As a result, in 2016, the FDA revised the black box warnings; while the labels for both drugs will still warn about the possibility of serious side effects on behavior and mood, these risks are considered to be "lower than previously suspected."

Concerns about side effects may be moot if varenicline turns out not to be very effective. Research has continued to support efficacy, although it is not always the case that varenicline alone is better than other treatments. One study found that smokers who wanted to quit—but had no current plans to actually try—were more likely to actually stop smoking if they were given Chantix versus a placebo (Ebbert et al., 2015). Combination treatment with varenicline and sustained-release bupropion for smokers who were not able to become abstinent with the nicotine patch was more effective than varenicline alone for male smokers and for smokers with a high degree of nicotine dependence (Rose and Behm, 2014). Adding a nicotine patch to varenicline treatment increased the success rate compared with varenicline alone (Coenraad et al., 2014). Among adults motivated to quit smoking, 12 weeks of open-label treatment with the nicotine patch, varenicline, or the patch plus a nicotine lozenge was comparable in rates of smoking abstinence at 26 weeks (19 to 21 percent by 52 weeks) (Baker et al., 2016). Some studies have provided evidence that perhaps varenicline would be more effective if given for a longer period of time (three or four weeks instead of just one week) before attempting smoking cessation (Ashare et al., 2012). Other studies have broadened the population for which varenicline treatment might be useful: it has been reported to be effective in helping smokeless tobacco users quit (Fagerström et al., 2010), in

be effective in helping smokeless tobacco users quit (Ragerstrom et al., 2016), in patients with schizophrenia or schizoaffective disorder (Jeon et al., 2016), and even in patients with depression (reported by the manufacturer, Pfizer, in 2012).

Perhaps the most scientifically interesting study involved the discovery that "normal" metabolizers of nicotine were significantly more likely to remain abstinent with varenicline compared to the nicotine patch for up to six months. In contrast, varenicline was equal to the nicotine patch at helping "slow" metabolizers quit, but there were more overall side effects reported with the drug. Medications like varenicline may be more effective in smokers who are normal metabolizers. This could be due to the fact that dopamine levels are increased by varenicline, which may reduce the cravings elicited by the rapid drop in nicotine experienced by normal metabolizers. In one such group of normal metabolizers, 22 percent of those on the patch were abstinent when the treatment was completed, versus almost 40 percent of those taking varenacline (Lerman et al., 2015).

Vaccine Therapy

A nicotine vaccine (similar to a cocaine vaccine; see Chapter 7) is one novel approach. Nicotine itself is a nonimmunogenic molecule and must be conjugated (attached) to a carrier protein to induce antibodies. The idea is that, once bound to antibodies, nicotine cannot cross the blood–brain barrier. This reduces its rewarding effect, which should promote abstinence. But a vaccine does not reduce the drug craving; it only blocks the drug's access to the brain.

Currently, two products, NicVAX and NIC002 (formerly NicQbeta) have been sufficiently tested. Results have been disappointing; none of the included studies detected a statistically significant difference in long-term cessation between participants receiving vaccine and those receiving placebo (Hartman-Boyce et al., 2012). Selecta Biosciences has taken over the project from the original company, Nabi. Selecta is using a slightly different technology involving synthetic vaccine particles (SVP), but has not yet started clinical trials.

Alternative Therapies to Smoking Cessation

Unfortunately, the long-term prognosis for smoking abstinence remains poor. Alpert and colleagues (2013) found that NRT products were no better in preventing

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Alternative Therapies to Smoking Cessation

Unfortunately, the long-term prognosis for smoking abstinence remains poor. Alpert and colleagues (2013) found that NRT products were no better in preventing relapse, even when used in conjunction with counseling (or combined with the opiate antagonist naltrexone (David et al., 2014)), than no treatment. These authors argue that public health policies, based on mass-media campaigns and no-smoking laws, are more effective in the long-term. Even in combination, drugs and

researchers have discovered an enzyme, NicA2, found in bacteria known as *Pseudomonas putida*, which lives in soils from tobacco fields. The bacteria depend on nicotine as their only source of the carbon and nitrogen they need to live. In testing the enzyme as a possible aid to smoking cessation, researchers added nicotine to a blood sample at a level corresponding to smoking one cigarette, then added the NicA2 enzyme. The half-life of the nicotine was reduced from 2 to 3 hours to 9 to 15 minutes. Higher doses, along with some chemical alterations, might even work faster, perhaps keeping nicotine in the blood from ever reaching the brain. The fact that the enzyme remained stable for up to three weeks at body temperature supports its development as a viable drug candidate (Xue et al., 2015).

One of the most unusual observations in regard to nicotine addiction was a report several years ago that some patients who were smokers and who had experienced a stroke in a part of the brain called the *insular cortex* had lost their desire to smoke. These patients were able to quit easily one day after surgery and did not have an urge to resume smoking. The involvement of this site in nicotine addiction has since been supported by experiments in rats, which have shown the phenomenon to be specific to the insular region (Pushparaj et al., 2013). Although unexpected, this accidental discovery may lead to new approaches to treating this difficult addiction.

A summary table of clinical guidelines for cessation of tobacco smoking, compiled by the Preventive Services Task Force, can be found at Siu et al. (2015).

This assignment will be a continuation of the written assignment from Week One. Research a minimum of three peer-reviewed articles in addition to information from your text on the disorder you chose in Week One. Consider the key classes of drugs used to treat the disorder you chose in Week One and explain their action at the neurotransmitter system involved in the disease process. Analyze and describe the agonist-antagonist activity of the drugs and the receptor types and subtypes involved in the disorder. Elaborate on the receptor agonist-antagonist actions of the drugs and describe the most common side effects seen with these drugs. Evaluate the risk-benefits of drug use for this disorder.

The paper:

- Must be three to five double-spaced pages in length, excluding title page and references page, and it must be formatted according to APA style as outlined in the Ashford Writing Center. (Links to an external site.)
- Must include a title page with the following:
  - Title of paper
  - Your name
  - Course name and number
  - Your instructor's name
  - Date submitted
- Must address the topic of the paper with critical thought.
- Must use at least three peer-reviewed sources in addition to the text.
- Must document all sources in APA style as outlined in the Ashford Writing Center.
- Must include a separate references page that is formatted according to APA style as outlined in the Ashford Writing Center.

This Disorder is Schizophrenia
I Have added only (1) Reference
From the Book, Need To use
Two more.

Text

Advokat, C. D., Comaty, J. E., & Julien, R. M. (2018). *Julien's primer of drug action: A comprehensive guide to the actions, uses, and side effects of psychoactive drugs* (14th ed.). Retrieved from https://vitalsource.com

Book Resource

CHAPTER 2

The Neuron, Synaptic Transmission, and Neurotransmitters

All our thoughts, actions, memories, and behaviors result from biochemical interactions that take place in and between *neurons*. Drugs that affect these processes are called *psychoactive drugs*. In essence, psychoactive drugs are chemicals that alter (mimic, potentiate, disrupt, or inhibit) the normal processes associated with neuronal function or communication between neurons. Therefore, to understand the actions of psychoactive drugs, it is necessary to have some idea of how the brain is organized, what a neuron is, and how neurons interact with each other.

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OVERALL ORGANIZATION OF THE BRAIN

The human nervous system consists of two divisions, the *central nervous system* (CNS) and the *peripheral nervous system* (PNS). The CNS includes the brain and the spinal cord; the PNS includes the nerves that originate in the spinal cord and that connect the spinal cord to the organs of the body. The drugs discussed in this book exert their primary actions and some of their side effects by acting in the brain. Many of their side effects, however, are produced by their actions in the PNS, that is, at various organ systems, such as the digestive system and the cardiovascular system, as described in subsequent chapters.

The human brain consists of perhaps 90 billion individual neurons located in the skull and the spinal cord. A flow chart of the brain is shown in Figure 2.1A with the three major divisions indicated: the *hindbrain*, the *midbrain*, and the *forebrain*. The hindbrain and forebrain are further divided into two subdivisions each, which results in five major sections. Figure 2.1B shows the anatomical arrangement of these structures.

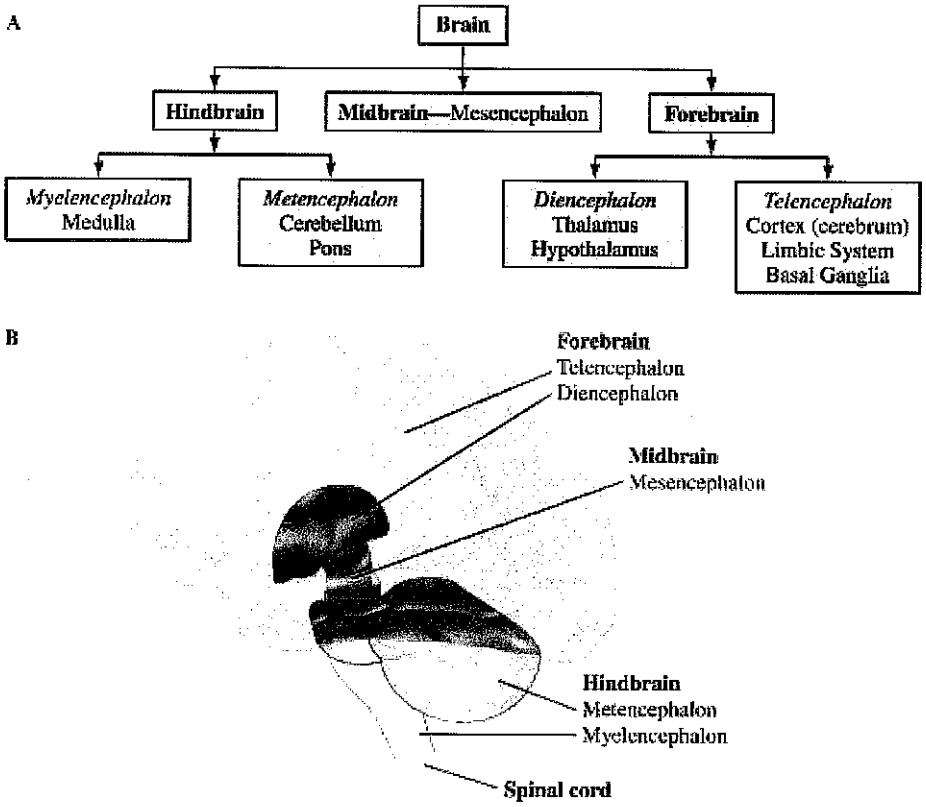

FIGURE 2.1 A. Flowchart of the brain and its major divisions. **B.** Outline of the human brain and its primary divisions.

The *spinal cord* is essentially the "information highway of the body" through which messages are sent back and forth between the brain and the rest of the body. This information includes touch, temperature, pain, joint position, and signals telling muscles to move.

Extending from the bottom of the brain (the medulla) to the sacrum (the bone in the lower part of the spine that forms the back of the pelvis), the spinal cord is made up of neurons and fiber tracts that

- Carry sensory information from the skin, muscles, joints, and internal body organs to the brain
- Modulate sensory input (including pain impulses)
- Organize and modulate the motor outflow to the muscles (to produce coordinated movement)
- Provide autonomic (involuntary) control of vital body functions

The part of the brain that is attached to the top of the spinal cord is the *brain stem* (Figure 2.2). It is divided into three parts: the *medulla* (its full name is the *medulla oblongata*), the *pons*, and the *midbrain*. All impulses that are conducted in either direction between the spinal cord and the brain pass through the brain stem, which is also important in the regulation of vital body functions, such as respiration (breathing), blood pressure, heart rate, gastrointestinal functioning, and the states of sleep and wakefulness. The brain stem is also involved in behavioral alerting, attention, and arousal responses. Depressant drugs, such as the barbiturates, depress the brain-stem activating system, which probably underlies much of their hypnotic action.

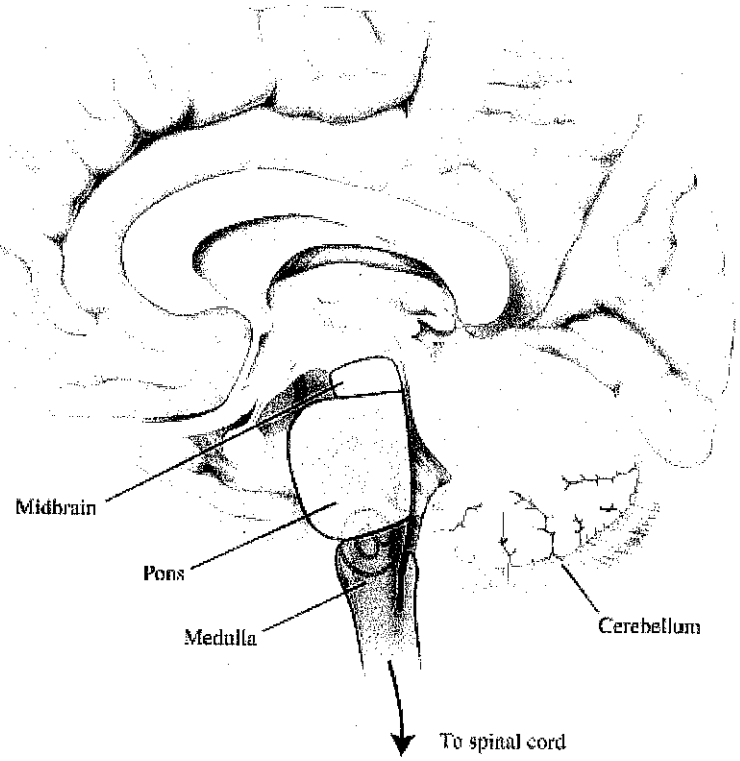

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FIGURE 2.2 The brain stem is the portion of the brain consisting of the medulla, pons, and midbrain, which connects the spinal cord to the forebrain.

Behind the brain stem is a large, bulbous structure — the *cerebellum*. A highly convoluted structure, the cerebellum is connected to the brain stem by large nerve tracts. The cerebellum is necessary for the proper integration of movement and posture. The staggering gait that is associated with drunkenness, termed *ataxia*

(loss of coordination and balance), is caused largely by an alcohol-induced depression of cerebellar function.

An important part of the brain stem, even though it is only about 2 centimeters long, is the midbrain, which sits between the forebrain and the hindbrain. The upper half (*tectum*, or "roof") contains pathways that carry sensory information, while the bottom half (*tegmentum*, or "floor") contains two important nuclei, which are connected, respectively, to two other systems, whose primary structures are located in the forebrain. The first of these nuclei, the ***substantia nigra***, is associated with the neuroanatomical system called the basal ganglia (discussed below; see Figure 2.4), which is responsible for coordination of movement and integration of motor control. Next to the substantia nigra is a more diffuse group of neurons called the ***ventral tegmental area*** (VTA), which is part of the neuroanatomical system called the ***reward circuit***, located in the limbic system (discussed below; see Figure 2.5). As will be discussed later, most of the neurons that make up these two midbrain nuclei contain the neurotransmitter dopamine.

The area immediately above the brain stem and covered by the cerebral hemispheres (cerebrum or cortex) is the ***diencephalon*** (Figure 2.3), consisting primarily of the thalamus and hypothalamus. The ***hypothalamus*** is a collection of neuronal structures near the junction of the midbrain and the thalamus just above the pituitary gland (whose function it modulates). There are 11 major nuclei that make up the hypothalamus and are responsible for the integration of our entire autonomic (involuntary or vegetative) nervous system. Thus, the hypothalamus controls such vegetative functions as eating and drinking, sleeping, regulation of body temperature, and sexual behavior, in large part by controlling the hormonal output of the pituitary gland. Neurons in the hypothalamus produce substances called *releasing factors*, which travel to the nearby pituitary gland, inducing the secretion of hormones that regulate such processes as the menstrual cycle in females and sperm formation in males. The hypothalamus is a site of action for many psychoactive drugs, either for the primary effect or for the side effects produced by the drug.

executive functions, such as working memory, planning, cognitive flexibility, and decision making, and the ventral-lateral prefrontal cortex is responsible for inhibition of motor functions, that is, neural basis of self-control.

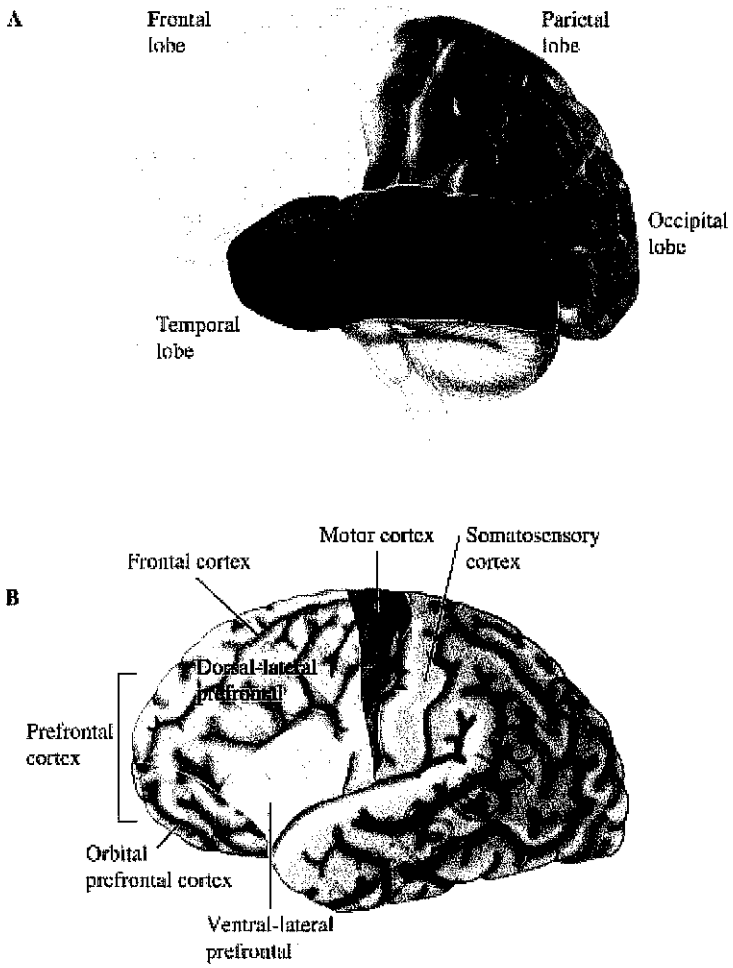

FIGURE 2.6 A. The cerebrum. The four major lobes of the human brain. **B.** Subdivisions of the frontal lobe, including the prefrontal cortex and its components: the orbital, the dorsal-lateral, and the ventral-lateral prefrontal cortex.

A particularly interesting structure is the insular cortex, or *insula*, a specific but hidden lobe of the brain located within the cerebral cortex, behind the temporal lobe and beneath the frontal and parietal lobes (Figure 2.7). It receives information about the physiological state of the body and integrates it into a broader context. For example, unpleasant smells or tastes may be reimagined as a sensation of

disgust. In 2007, it was reported that some people with damage to the insula were able to give up cigarettes instantly.

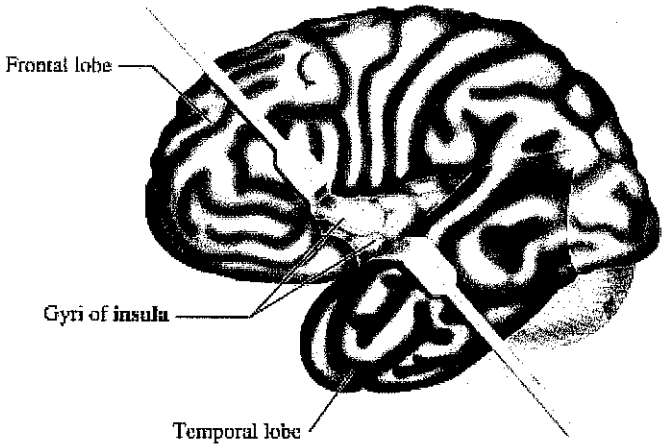

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FIGURE 2.7 The Insula.

There is a special cell type in the insula, the Von Economo neurons, names for the neuroscientist who discovered them in 1925. For this reason, they are known as VENs. In addition to the frontal insula, these unusually large, cigar-shaped cells are also located in the anterior cingulate cortex. Aside from humans, only whales, great apes, and elephants are known to have them (Blakeslee, 2007).

In the last few years, there have been some remarkable technological developments in the neuroscience of the brain, especially in regard to understanding the neural basis of behavior. One significant international initiative is the Human Connectome Project (HCP). With start-up funding of $40 million, this collaboration began in 2010 with the goal of determining how neurons are connected across numerous brain sites. The first dataset was released in April 2015. This result consisted of connectomes obtained from about 460 people, 22 to 35 years old. In addition to the anatomical results, the outcome included information about personality variables, various intelligence assessments, social and economic conditions, and history of drug use, as well as age. The eventual goal is to collect data from 1200 adults in order to determine which systems across the brain are functioning while the brain is quiet. The connectomes are thought to indicate those neuronal associations that remain active to keep the brain ready to perform certain functions (Figure 2.8) (Reardon, 2015).

In addition to the frontal insula, these unusually large, cigar-shaped cells are also located in the anterior cingulate cortex. Aside from humans, only whales, great apes, and elephants are known to have them (Blakeslee, 2007).

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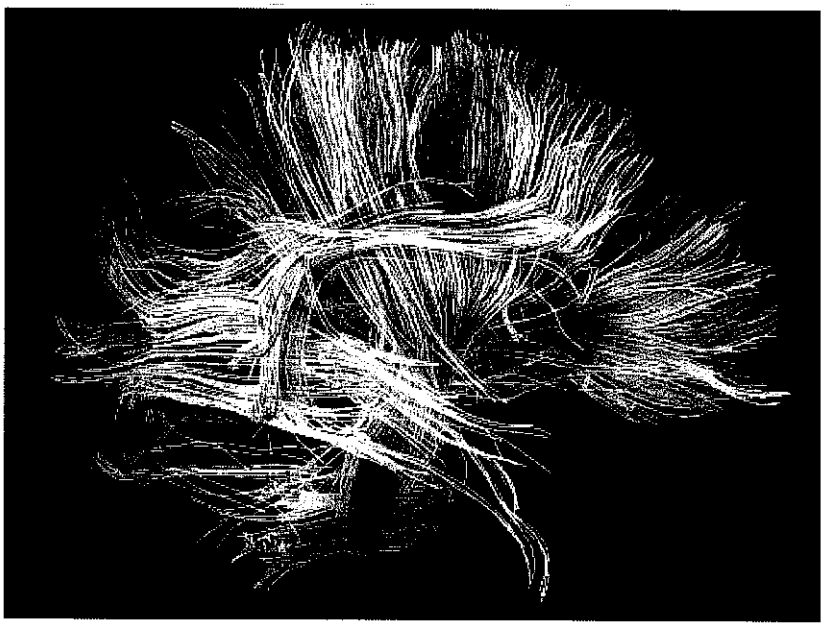

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FIGURE 2.8 A connectome of the brain shows active connections between neurons.

In July 2016, progress made by the HCP was made public with the publication of a new map of the brain, which contained nearly 100 previously unknown regions

(Zimmer, 2016). The map was created by applying complex computer analyses to the large amount of data collected from the test subjects. Each participant had their brain mapped while they underwent hours of memory, language, and other neuropsychological tests. This update is the first large-scale revision of the cortex since 1907, when an atlas of 52 brain regions was published by Korbinian Brodman. According to one of the investigators, there were 112 different types of information used to construct the new map, including anatomical data, such as the amount of myelin, as well as the neuropsychological test results. (You can see the latest developments at www.humanconnectomeproject.org.)

OVERVIEW OF SYNAPTIC TRANSMISSION

The central nervous system (CNS) is made up of two types of cells: neurons and a variety of nonneural cells, collectively called *glia* (from the Greek word meaning "glue"). It had long been thought that glia are more abundant than neurons and that there were from 10 to 50 times more glia than neurons in the CNS. There is recent evidence, however, that the 10:1 glia to neuron ratio is a myth and that the ratio in human and other primate brains is much closer to 1:1. It turns out to be more difficult to determine the ratio of glia to neurons than you might think. For example, some parts of the human brain have a higher ratio than others, and the ratio of other species differs from that of humans (Yuhas and Jabr, 2012).

The neuron is the basic functional unit, while glia provide support and protection. The main types of glial cells in the CNS are oligodendrocytes, astrocytes, and ependymal and microglial cells. Although glia may turn out to be less numerous than previously thought, they may in fact be more important than previously believed. Oligodendrocytes form the myelin sheath around axons. Astrocytes provide neurons with nutrients and structural support. They maintain the extracellular environment of neurons by regulating their ionic surroundings, modulating the rate of signal transmission and the reuptake of neurotransmitters. Astrocytes play a crucial role in synapse formation and they affect (by promoting or preventing) recovery after neural injury. Microglia are involved in cleaning up damaged cells and debris and pruning neurons. Recent research suggests that they may be involved in disorders such as schizophrenia and Alzheimer's because of extensive pruning leading to massive synaptic loss (Hong et al., 2016).

A typical neuron has a *soma* (cell body), which contains the nucleus (including the genetic material of the cell) and several other structures, or *organelles*, that perform vital functions (Figure 2.9A). For example, mitochondria produce energy from nutrients, while Golgi bodies package substances (such as neurotransmitters) into vesicles for storage.

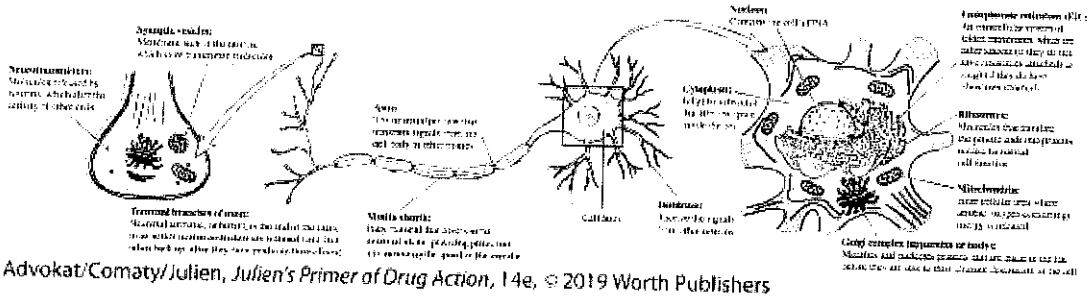

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FIGURE 2.9 Major parts of a neuron. Within the cell body is the nucleus, which contains the genetic code, DNA. The cell body is filled with a gelatinous substance, the cytoplasm. Within the cytoplasm are various organelles, which perform specific functions. The endoplasmic reticulum is a network of flattened sacs and branching tubules that extends throughout the cytoplasm, which provides a platform for ribosomes and a mechanism of transportation for movement of cellular products. Ribosomes synthesize proteins, mitochondria produce energy for cell functions, and the Golgi complex combines simple molecules into more complex structures and packages them into vesicles. Dendrites and axons are processes that receive incoming signals and send outgoing messages, respectively. Some axons are protected by myelin, a fatty sheath. The axons end in terminals, which contain membrane sacs filled with transmitter molecules.

Extending from the soma in one direction are many short fibers, called *dendrites*, which receive input from other neurons through *receptors* located on the dendritic membrane (see Figure 2.9B). When a signal arrives from another cell, a message is generated and travels down the dendrite to the soma. Extending in another direction from the soma is a single process called an *axon*, which can vary in length from a few millimeters up to a meter (such as those that run from the motor neurons of the spinal cord out to the muscles that they stimulate). The axon transmits the signal through an electrochemical process (the *action potential)* from the soma to other neurons or to muscles, organs, or glands of the body. Longer axons are usually covered with a *myelin sheath*, produced by specialized types of glia, which increases the speed of the signal.

Information flows from the axon to the next neuron or cell by way of a specialized structure called *a synapse*. According to Thompson (1993), a "given neuron in the brain may receive ... thousand(s) of connections from other neurons" and the "number of possible different combinations of synaptic connections among

the neurons in a single human brain is larger than the total number of atomic particles that make up the known universe. Hence the diversity of the interconnections in a human brain seems almost without limit" (2–3).

It was once thought that the brain has the maximal number of neurons at birth and that once a neuron dies, it is not replaced. This concept has been revised because we now realize that new neurons form every day (a process called *neurogenesis*) (Kempermann et al., 2004; Schaffer and Gage, 2004). Synaptic contacts between neurons are continually being reshaped, with axon terminals and dendrites re-forming new synaptic connections while eliminating old ones. This remodeling probably begins even before birth and continues throughout our lives.

A synapse consists of the presynaptic membrane (typically the axon terminal) of one neuron, the postsynaptic membrane of the receiving neuron (which might be a dendrite, the soma, or the axon terminal of another neuron), and a minute space (the *synaptic cleft*) between them (Figure 2.10). Among the numerous structural elements of the presynaptic side (for our purposes) are the synaptic vesicles, each of which contains several thousand neurotransmitter molecules that transmit information from one neuron to another. These vesicles serve two functions. They store the transmitter and protect it from being destroyed by metabolic enzymes so that it is available for release. When the action potential reaches the axon terminal, it triggers a series of biochemical actions, which cause the vesicles to fuse with the presynaptic membrane and release the transmitter, a process called *exocytosis*. The transmitter molecules diffuse across the synaptic cleft and attach to various types of structures, called *receptors*, on both the presynaptic terminal and the postsynaptic membrane of the next neuron (see Chapter 3). The neurons do not physically touch each other; synaptic transmission is a chemical rather than an electrical process. Recently, however, it has been reported that, in at least some synapses, special proteins are arranged on the pre- and postsynaptic membranes such that the neurotransmitter molecules are aligned opposite their receptor sites. These structures, termed *nanocolumns*, appear to connect regions of neurotransmitter molecule release and activation (Tang et al., 2016).

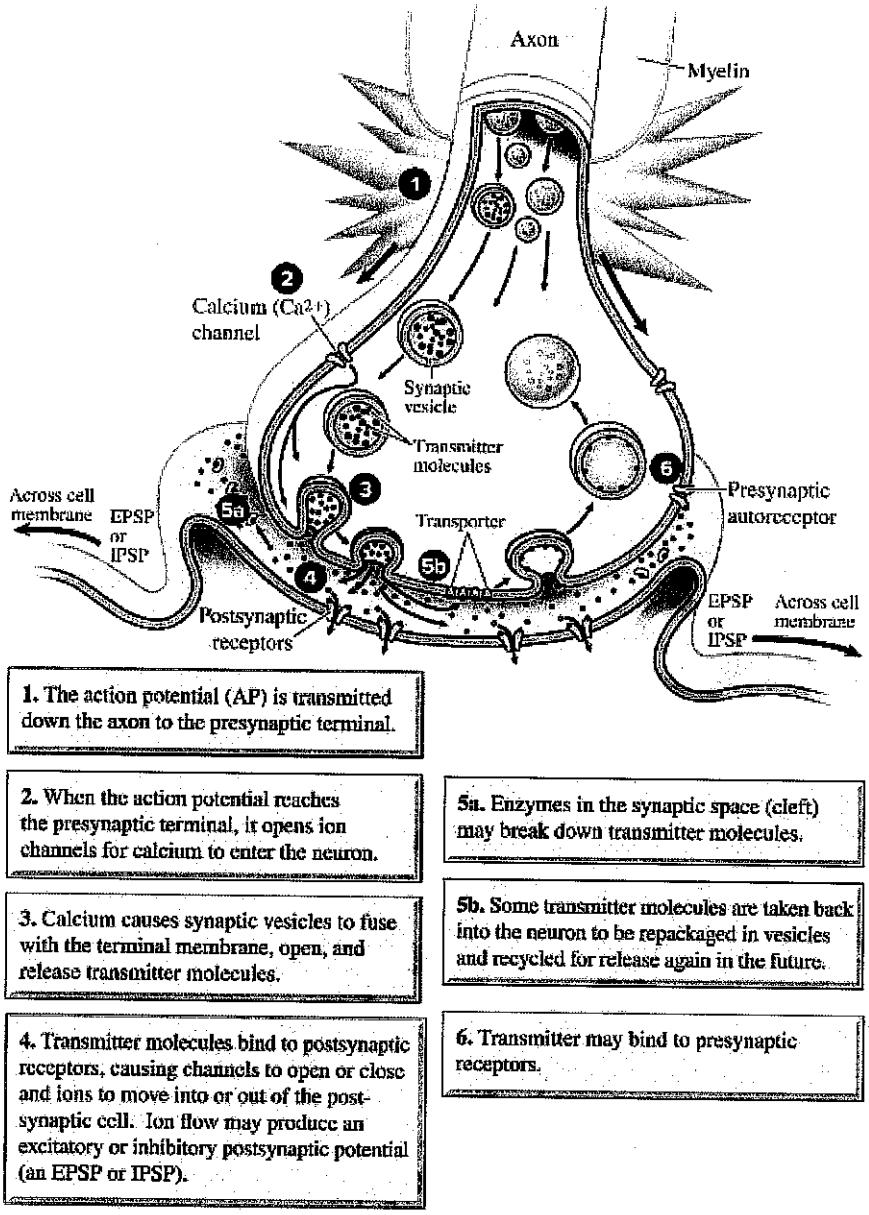

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FIGURE 2.10 Structure and function of a generic synapse. Neurotransmitter is produced (synthesized) and stored in vesicles within the axon terminal. When an action potential reaches the terminal, it causes channels to open so that calcium can enter and initiate *exocytosis* (release of transmitter molecules) into the synaptic cleft. After release, neurotransmitter molecules bind to and activate receptors on the pre- and postsynaptic membrane. Transmitter effects are terminated either by breakdown of transmitter within the synaptic cleft or by reuptake back into the axon terminal to be recycled.

Synaptic transmission is remarkably fast; the entire process may occur over a time span as short as a millisecond for transmitter release (from presynaptic

vesicles), diffusion (across the cleft), receptor attachment, and activation. The nature of the response produced by synaptic transmission depends on the characteristics of the receptor that is activated (see Chapter 3). Receptors may respond quickly, within milliseconds, or they may produce responses that last hundreds of milliseconds. The ultimate outcome of receptor activation is a function of the organ or tissue in which it is located. In summary, the arrival of an action potential at the axon terminal induces release of a neurotransmitter into the synaptic cleft and the transmitter then activates its receptors.

The release of neurotransmitter may be modulated by presynaptic receptors, termed *autoreceptors* (see Figure 2.10). An autoreceptor is a presynaptic site on a neuron that binds the neurotransmitter *released by that neuron.* These receptors regulate the neuron's activity. Autoreceptors serve as negative feedback mechanisms. When stimulated by transmitter or by certain drugs, these receptors *reduce* the synthesis and further release of transmitter. Thus, when large amounts of transmitter are present in the synaptic cleft, excess transmitter molecules act on the autoreceptors to decrease further production and release. Conversely, if an antagonist blocks an autoreceptor, synthesis and release of transmitter is increased.

Once release has occurred, there must be a way to get rid of neurotransmitter; otherwise, transmitter would stay in the synaptic cleft and continually bind to and activate receptors. In most cases, transmitter removal occurs through one of two general types of mechanisms (see Figure 2.10; with some variations as described below for specific transmitters):

1. An enzyme present in the synaptic cleft breaks down any neurotransmitter remaining in the synapse. The metabolites are then taken back up into the presynaptic neuron to be resynthesized and repackaged for release. This is how the effect of the neurotransmitter acetylcholine is terminated. Drugs used in the treatment of Alzheimer's disease act by blocking this process, thereby increasing the amount of acetylcholine in the synapse, which may delay the progression of the dementia (see Chapter 16).
2. The transmitter itself is taken back into the presynaptic neuron and repackaged. The action of the neurotransmitters dopamine, norepinephrine, and serotonin is terminated by this mechanism. Drugs that block this reuptake process represent one class of antidepressant medication. In an alternative version of this process, transmitter is taken up into an adjacent glial cell and metabolized. The metabolites are then recycled back to the neuron where they are resynthesized into neurotransmitter and repackaged for release. The effect of the transmitter glutamate is terminated by this method.

was identified as a transmitter chemical first in the peripheral nervous system and later in brain tissue. Deficiencies in acetylcholine-secreting neurons have classically been associated with the dysfunctions seen in Alzheimer's disease. Certainly drugs that either potentiate or inhibit the central action of acetylcholine exert profound effects on memory. For example, scopolamine is a psychedelic drug that blocks central cholinergic receptors and as a result produces amnesia. Conversely, drugs that increase the amount of acetylcholine in the brain appear to improve memory function and are used to delay the progression of Alzheimer's disease.

Acetylcholine is synthesized in a one-step reaction from two precursors (choline and acetyl coenzyme A) and then stored within synaptic vesicles for later release (Figure 2.11). Like other neurotransmitters, acetylcholine is released into the synaptic cleft, rapidly diffuses across the cleft, and reversibly binds to postsynaptic receptors. Once acetylcholine has exerted its effect on postsynaptic receptors, its action is terminated by the enzyme *acetylcholinesterase* (AChE), which is located in the postsynaptic side of the synaptic cleft.

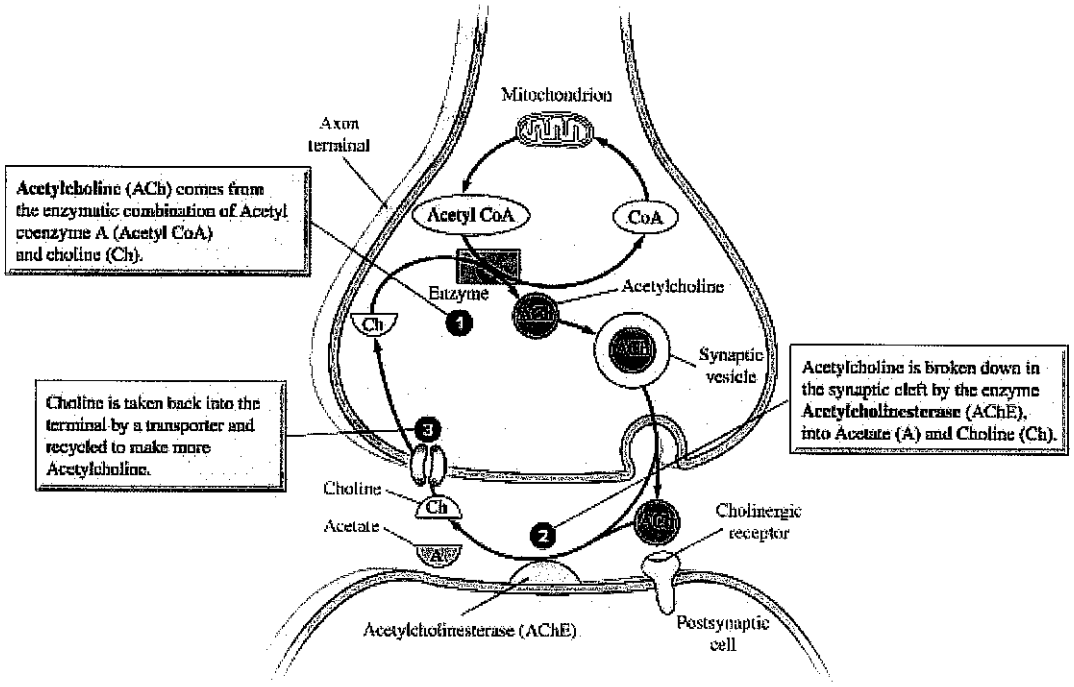

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FIGURE 2.11 Schematic of an acetylcholine (ACh) synapse. Acetylcholine is made in the axon terminal from acetyl coenzyme A (acetyl CoA) and choline and stored in vesicles for release. After release, acetylcholine binds to its receptors and is immediately broken down at the receptors by acetylcholinesterase (AChE) into choline and acetate.

The enzymatic reaction that degrades acetylcholine is important not only in the treatment of Alzheimer's disease, but also in agriculture and the military. Drugs that block the action of acetylcholinesterase, referred to as *AChE inhibitors,* include both "reversible" and "irreversible" compounds. *Irreversible AChE inhibitors* form a permanent covalent bond with the enzyme and totally inhibit enzyme function. They are usually administered in "toxic" doses and the result is usually fatal. Some of these toxic drugs (such as *malathion* and *parathion*) have been exploited in gardening and agriculture as insecticides because they kill insects on contact. Other irreversible AChE inhibitors (such as *sarin* and *soman*) have been used in the military as lethal nerve gases.

Less toxic and shorter acting are the *reversible AChE inhibitors.* They are used clinically as putative cognitive enhancers to delay memory decline in patients with Alzheimer's disease. Individual agents are discussed in Chapter 16.

Cholinergic receptors are subclassified into two categories, nicotinic and muscarinic, named for substances that specifically stimulate each category. Muscarinic receptors are the "slow" type (metabotropic), while nicotinic receptors are the "fast" type (or ionotropic; see Chapter 3). They can be found on both sides of the synaptic cleft (presynaptic and postsynaptic). Muscarinic receptors bind acetylcholine and muscarine, a substance found in certain poisonous mushrooms. (It was first isolated in *Amanita muscaria.*) Binding studies have identified five subclasses of muscarinic receptors: M_1, M_2, M_3, M_4, and M_5. M_1, M_4, and M_5 are involved in complex CNS responses such as memory, arousal, attention, and analgesia. M_2 are on heart muscle and when stimulated, they slow the heart rate; M_3 are found on a variety of involuntary muscles, such as the bladder and lungs. Nicotinic receptors (nAChR) are subdivided into two types: N_1 (or N_M), found on the voluntary, or skeletal, muscles, and N_2 (or N_N), found in the nervous system and in the adrenal glands.

Acetylcholine is distributed widely in the brain (Figure 2.12). The cell bodies of cholinergic neurons in the brain lie in two closely related regions. One involves the *septal nuclei* and the *nucleus basalis.* The axons of these neurons project to forebrain regions, particularly the hippocampus and cerebral cortex. The second group of acetylcholine neurons originates in the midbrain region and projects anteriorly (forward) to the thalamus, basal ganglia, and diencephalon (not shown in the figure) and posteriorly (backward) to the medulla, pons, cerebellum, and cranial nerve nuclei. In addition to its generally accepted role in learning and

is consistent with suggestions that acetylcholine is involved in circuits that modulate sensory reception; in mechanisms related to behavioral arousal, attention, energy conservation, and mood; and in REM (rapid eye movement) activity during sleep (dreaming).

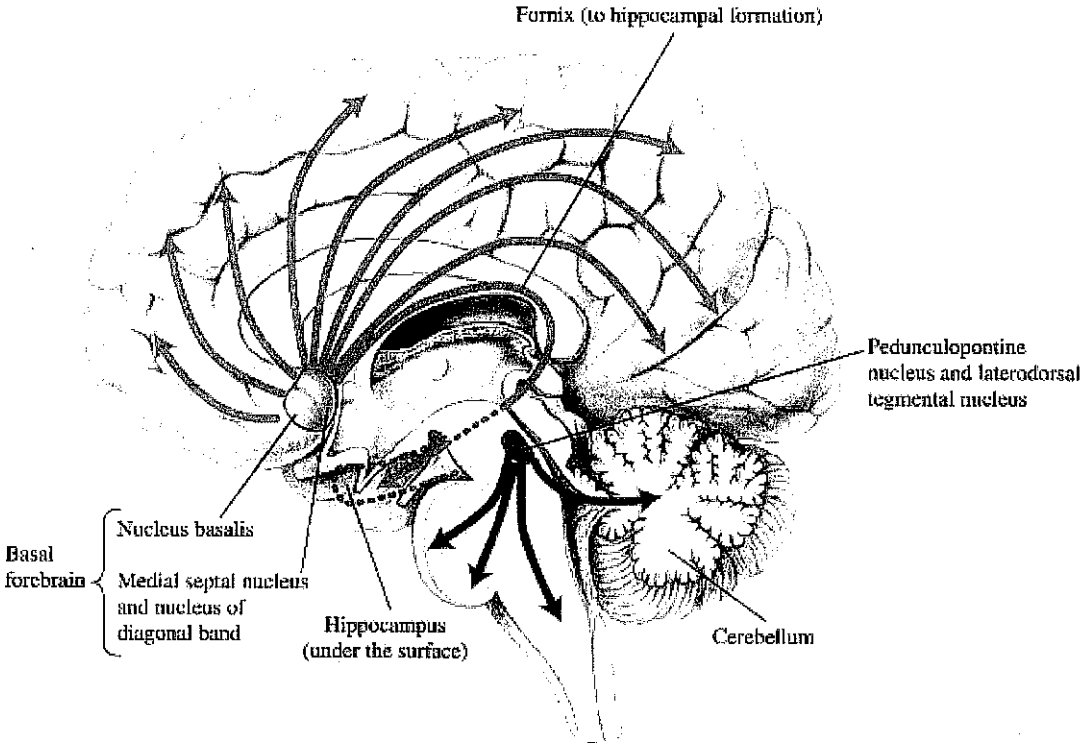

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FIGURE 2.12 The two major cholinergic systems in the human brain. The basal forebrain cholinergic complex composed of neurons in the medial septal nucleus and nucleus basalis, which projects to the telencephalon; the pontomesencephalotegmental cholinergic complex, composed of cells in the pedunculopontine and laterodorsal tegmental nuclei, which ascend to the thalamus and other diencephalic loci (not shown) and descend to the pons, medulla, cerebellum, and cranial nerve nuclei.

MONOAMINERGIC NEUROTRANSMITTERS

Catecholamine Transmitters: Dopamine and Norepinephrine

The term *catecholamine* refers to compounds that contain a catechol nucleus (a benzene ring with two attached hydroxyl groups) to which is attached an amine group (Figure 2.13). In the CNS, the term usually refers to the transmitters *dopamine* (DA) and *norepinephrine* (NE). In the peripheral nervous system, *epinephrine* (adrenaline) is a third catecholamine transmitter. In the brain, a large number of psychoactive drugs (both licit and illicit, therapeutic and abused) exert their effects by altering the synaptic action of norepinephrine and dopamine.

The chemical synthesis of the catecholamines is illustrated in Figure 2.13. Biosynthesis of the catecholamines begins with the amino acid tyrosine (found in foods such as egg whites, cottage cheese, soy products, meat, fish, poultry, mustard greens, and spinach) and involves several steps controlled by specific enzymes. Following synthesis, these transmitters are stored in vesicles for release into the synaptic space. After release, norepinephrine and dopamine attach to pre- and postsynaptic receptors and initiate responses in the receiving cell or neuron. As noted earlier, inactivation occurs primarily by reuptake of the transmitter from the synaptic cleft into the presynaptic nerve terminal. Within the nerve terminal, catecholamines may be inactivated by enzymes such as *monoamine oxidase* (MAO). The class of antidepressants referred to as MAO inhibitors (MAOIs; see Chapter 12) acts by blocking monoamine oxidase, thereby increasing the amounts of dopamine and norepinephrine available for synaptic release.

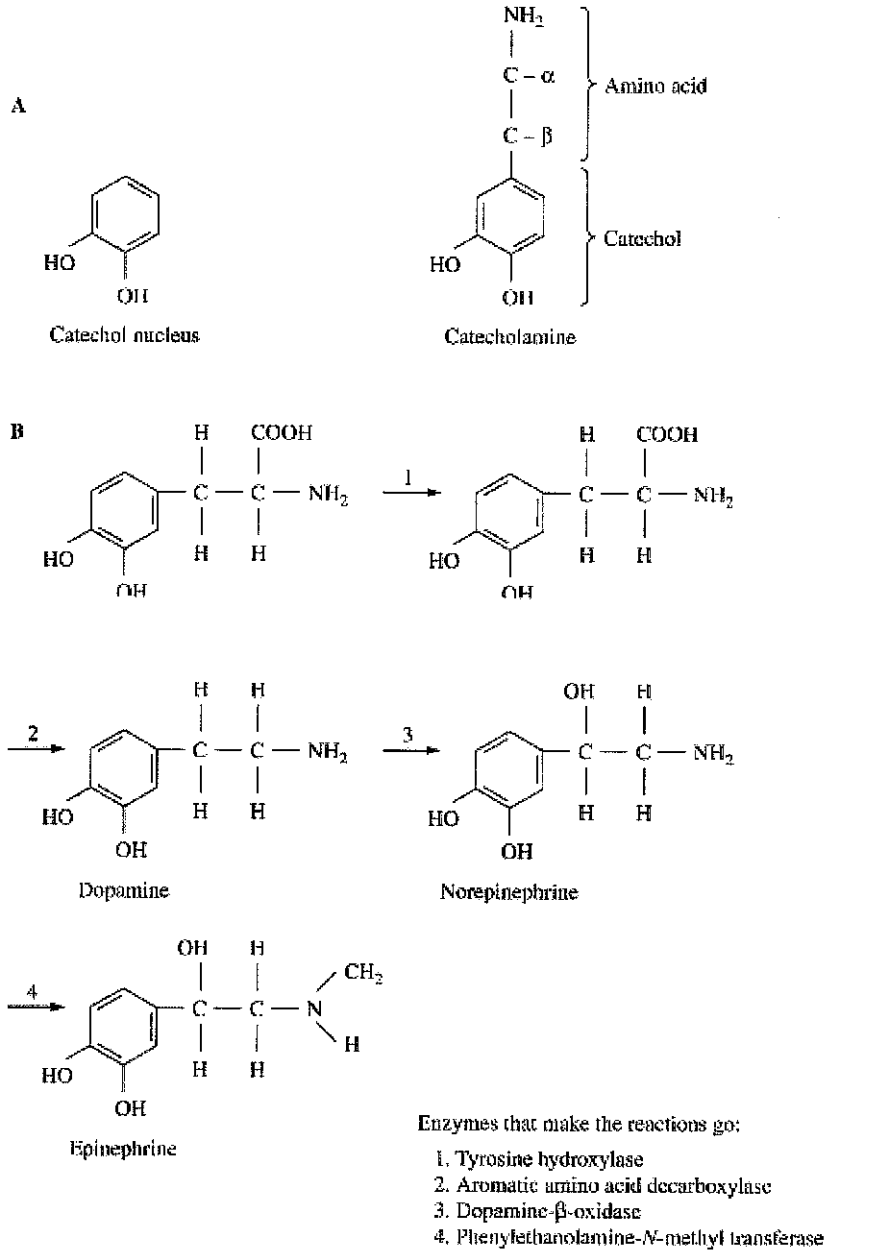

FIGURE 2.13 A. Catechol and catecholamine structure. All catecholamines share the catechol nucleus, a benzene ring with two adjacent hydroxyl (OH) groups. **B.** Structures and synthesis of the catecholamines. Tyrosine, an amino acid found in foods, is converted into dopa, then into dopamine, next into norepinephrine, and finally (in the peripheral nervous system) into epinephrine, depending on which enzymes (one to four) are present in the cell.

Catecholamine Receptors

Each catecholamine transmitter exerts effects on a number of different receptors. Norepinephrine and epinephrine act on two primary types of receptors (alpha and beta), each of which has at least two subtypes. Dopamine exerts postsynaptic effects on at least six receptors, divided into two families (D_1 type and D_2 type). The D_1 receptor family consists of two subtypes — D_1 and D_5 — and the D_2 receptor family consists of four subtypes — D_{2A}, D_{2B}, D_3, and D_4. Postsynaptic dopamine receptors of the D_2 family are responsible for at least part of the antipsychotic activity and side effects of the drugs discussed in Chapter 11. Alterations in dopamine receptor function have been implicated in numerous diseases and behavioral states, including schizophrenia, parkinsonism, affective disorders, sexual activity, addiction, and attention deficit/hyperactivity disorder.

Norepinephrine Pathways

The cell bodies of norepinephrine neurons are located in the brain stem, mainly in a structure in the pons called the *locus coeruleus* (Figure 2.14). From there, axons project widely throughout the brain to nerve terminals in the cerebral cortex, the limbic system, the hypothalamus, and the cerebellum. Axonal projections also travel down the spinal cord, where they exert an analgesic action. The release of norepinephrine produces an alerting, focusing, orienting response, positive feelings of reward, and analgesia.

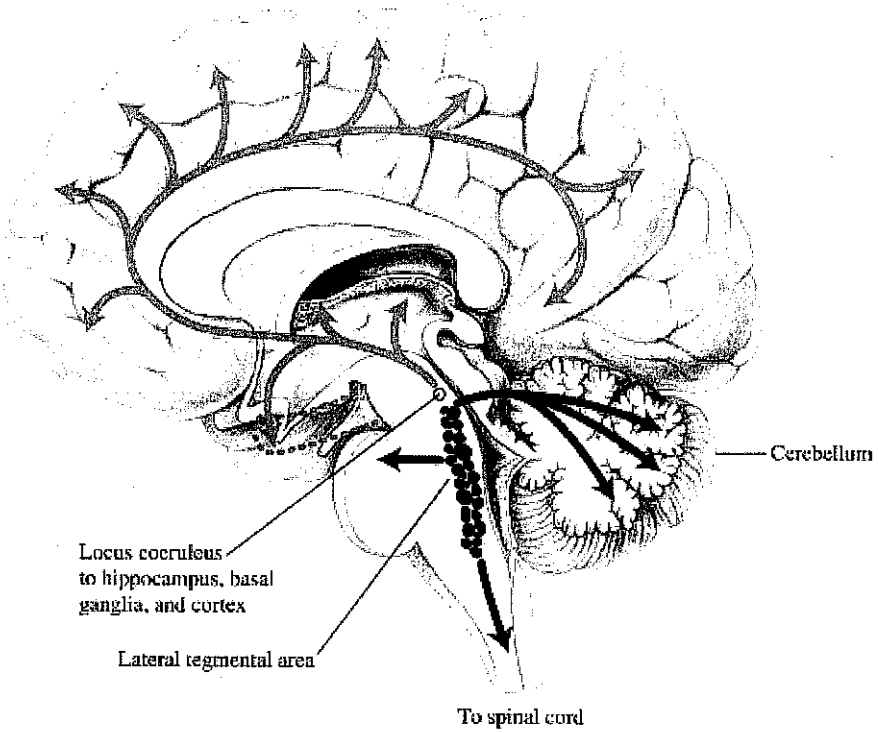

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FIGURE 2.14 Noradrenergic projection systems in the human brain. The cell bodies are in the locus coeruleus and adjacent regions of the brain stem and project widely to the forebrain and cerebellum and to the brain stem and spinal cord.

Dopamine Pathways

Dopamine pathways also originate in the brain stem, sending axons both rostral (forward) to the brain and caudal (backward) to the spinal cord (Figure 2.15). Three dopamine circuits are most relevant for our discussions:

1. Neurons in the hypothalamus send short axons to the pituitary gland (not shown in Figure 2.15). These neurons regulate certain hormones. Alterations in hormone function are commonly seen in people with schizophrenia who are taking various antipsychotics, which block these dopamine receptors (see Chapter 11).
2. Neurons in the substantia nigra (see Figure 2.15) that project to the basal ganglia (see Figure 2.4) play a major role in the regulation of movement. As noted earlier, parkinsonism (see Chapter 16) and parkinsonian side effects produced by antipsychotic drugs (which block these receptors) (see Chapter 11) all involve this pathway.

3. Cell bodies of the VTA in the midbrain are located next to the substantia nigra (see Figure 2.15). Dopamine neurons of this nucleus extend forward and separate into two pathways. One branch, called the *mesocortical*, projects to the frontal cortex, and a second branch, called the *mesolimbic*, projects to the limbic system. These two dopaminergic pathways are extremely important in psychopharmacology. First, alterations in the development of these pathways may be involved in the pathogenesis of schizophrenia and its amelioration by antipsychotic drugs. That is because, as discussed in Chapter 11, drugs used in the treatment of schizophrenia all share the common action of blocking dopamine receptors in this pathway. Second, these dopaminergic pathways also include structures that are activated by drugs (and other stimuli) that produce sensations of pleasure. This group of structures constitutes our "central reward circuit," which is involved in addiction to most drugs of abuse (discussed in Chapter 4).

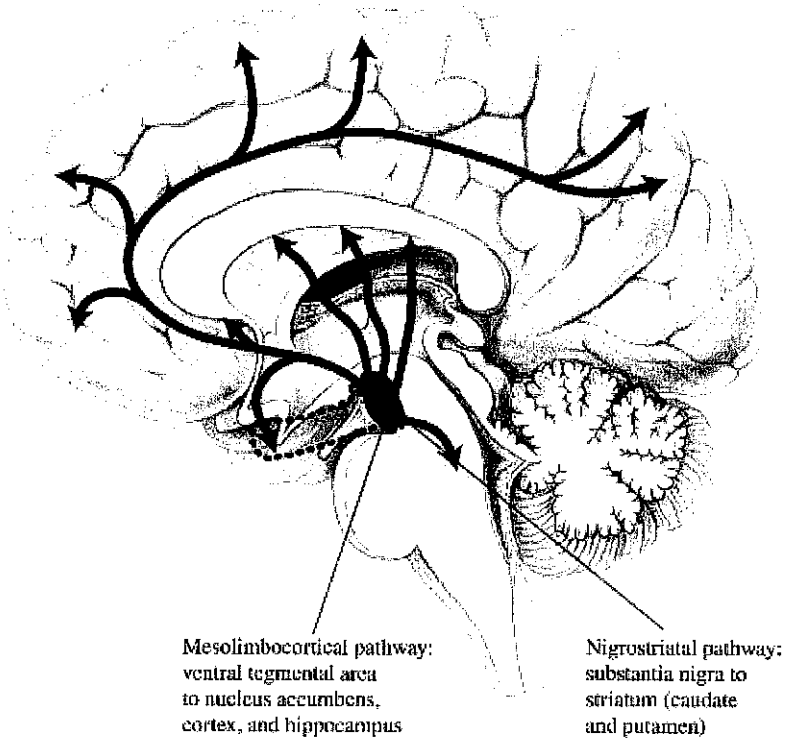

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FIGURE 2.15 There are three major dopamine systems in the brain. One is a local circuit in the hypothalamus (not shown); another, the nigrostriatal pathway, projects from the substantia nigra to the caudate nucleus of the basal ganglia and is involved in motor functions and Parkinson's disease; the third consists of cell bodies next to the substantia nigra in the midbrain that project widely to the cerebral cortex and forebrain limbic system.

was first investigated as a CNS neurotransmitter in the 1950s when lysergic acid diethylamide (LSD) was found to resemble serotonin structurally and block the contractile effect of serotonin on the gastrointestinal tract. At that time, it was hypothesized that LSD-induced hallucinations might be caused by alterations in the functioning of serotonin neurons and that serotonin might be involved in abnormal behavioral functioning. Today, drugs that potentiate the synaptic actions of serotonin are widely used as antidepressants and as antianxiety agents (specifically, the serotonergic agents known as *selective serotonin reuptake inhibitors*, or SSRIs; see Chapter 12). Serotonin plays a role in depression, anxiety and obsessive-compulsive disorder, panic, phobias, sleep, sex, cardiovascular function, and the regulation of body temperature; use of an SSRI to treat depression can be associated with such side effects as insomnia, anxiety, and loss of libido.

Significant amounts of serotonin are found in the upper brain stem, particularly in the pons and the medulla, in structures collectively called the *raphe nuclei.* Anterior projections from the brain stem terminate diffusely throughout the cerebral cortex, hippocampus, hypothalamus, and limbic system (Figure 2.16). Serotonin projections largely parallel those of DA, although they are not as widespread. Axons of serotonin neurons descending to the spinal cord from cell bodies located in the raphe nuclei may be involved in the modulation of both pain and spinal reflexes.

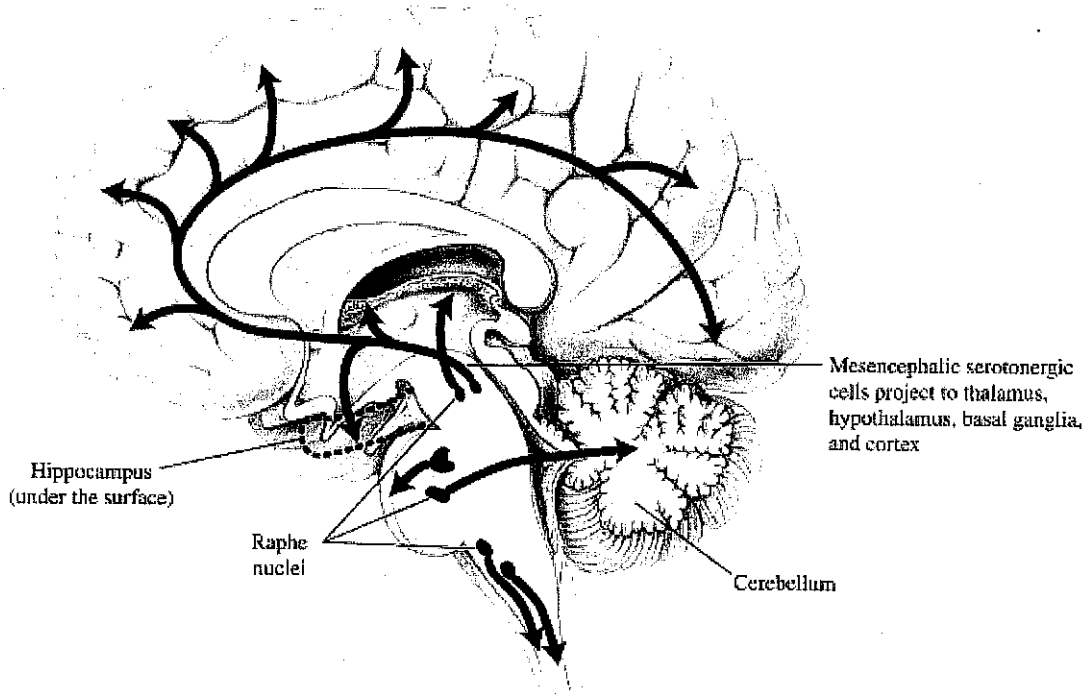

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FIGURE 2.16 Serotonin pathways in the human brain.

Serotonin is an indoleamine. Indoleamines all contain indole groups, a benzene ring (six-carbon ring) fused to a pyrrole ring (five-membered ring with four carbons and a nitrogen). Serotonin is synthesized in the brain from the essential amino acid tryptophan (Figure 2.17A). Because the human body cannot make tryptophan, we must get it from the foods we eat, such as poultry, bananas, tomatoes, and walnuts. Serotonin is produced by a short metabolic pathway consisting of two enzymes: tryptophan hydroxylase and amino acid decarboxylase.

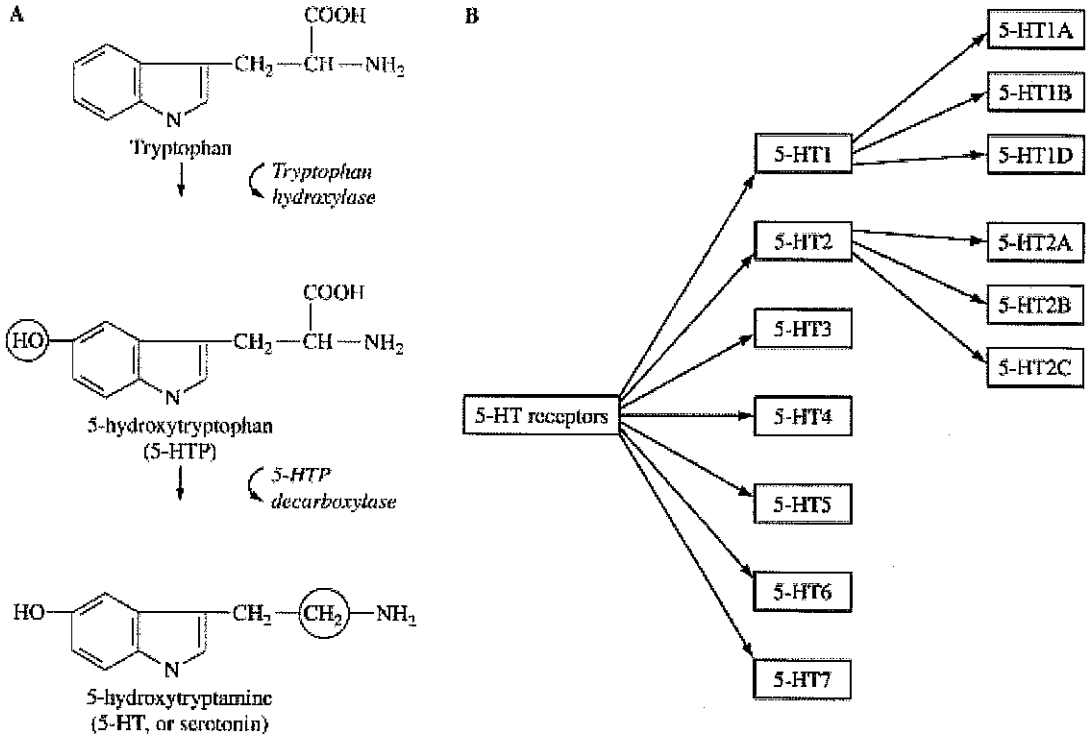

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FIGURE 2.17 A. Biosynthesis of serotonin. B. Serotonin receptor nomenclature.

Several chemically distinct serotonin (5-HT) receptors have been identified. They have been classified in families (designated by a number) and subtypes within a family (designated by a letter). The main families and subtypes of 5-HT receptors are shown in Figure 2.17B. There are 14 different known 5-HT receptors. In 2013, the structures of two of these were uncovered using X-ray crystallography, by which X-ray beams are fired at crystals of the compound, and the way in which the beams are scattered can allow scientists to determine the structure. The studies found that 5-HT receptors 1B and 2B had similar structures where serotonin binds, but that this space was larger in 1B than in 2B. Although only the width of three helium atoms, this difference was enough to explain why the two receptors bind differently to different drugs. This may be very important for drug safety: because some drugs that stimulate 2B receptors are thought to cause heart problems, it has been nicknamed the "death receptor" (Wang et al., 2013).

Amino Acid Neurotransmitters

There are two amino acid neurotransmitters that are widely distributed in the brain. The first, *glutamic acid* (or *glutamate*), is the major universally excitatory neurotransmitter; the second is *gamma aminobutyric acid* (GABA), which is the major inhibitory neurotransmitter. Most other amino acids in the brain do not serve as neurotransmitters (with the exception of aspartate and glycine), but function as precursor molecules for the biosynthesis of other transmitters (for example, tyrosine for catecholamines and tryptophan for serotonin).

Both glutamate and GABA function to modulate a number of receptors, maintaining a balance between excitation and inhibition in the brain. The following sections focus on glutamate and GABA, because they are involved in the actions of several psychoactive drugs, ranging from the benzodiazepine antianxiety agents (see Chapter 13) to the mood stabilizers (see Chapter 14).

Glutamate

Glutamate is the major excitatory neurotransmitter in the brain and is also the precursor for the major inhibitory neurotransmitter GABA. GABA is formed from glutamate under control of the enzyme *glutamic acid decarboxylase.*

Glutamate is a nonessential amino acid, meaning that it is easily synthesized in the body and is not required in the diet. It does not readily penetrate the blood–brain barrier and is produced locally by specialized neuronal mechanisms. It can be synthesized by a number of different chemical reactions, among which is the normal breakdown of glucose. A second reaction, which might be the more important for neuronal glutamate, involves a glutamine cycle in which synaptically inactive glutamine serves as a reservoir of glutamate (Figure 2.18). In this process, after glutamate is released from a neuron and exerts its excitatory effect, it is transported into astrocytes and converted to glutamine. Eventually, the glutamine diffuses out of the astrocytes and enters the presynaptic nerve terminals, where it is converted to glutamate, the active neurotransmitter.

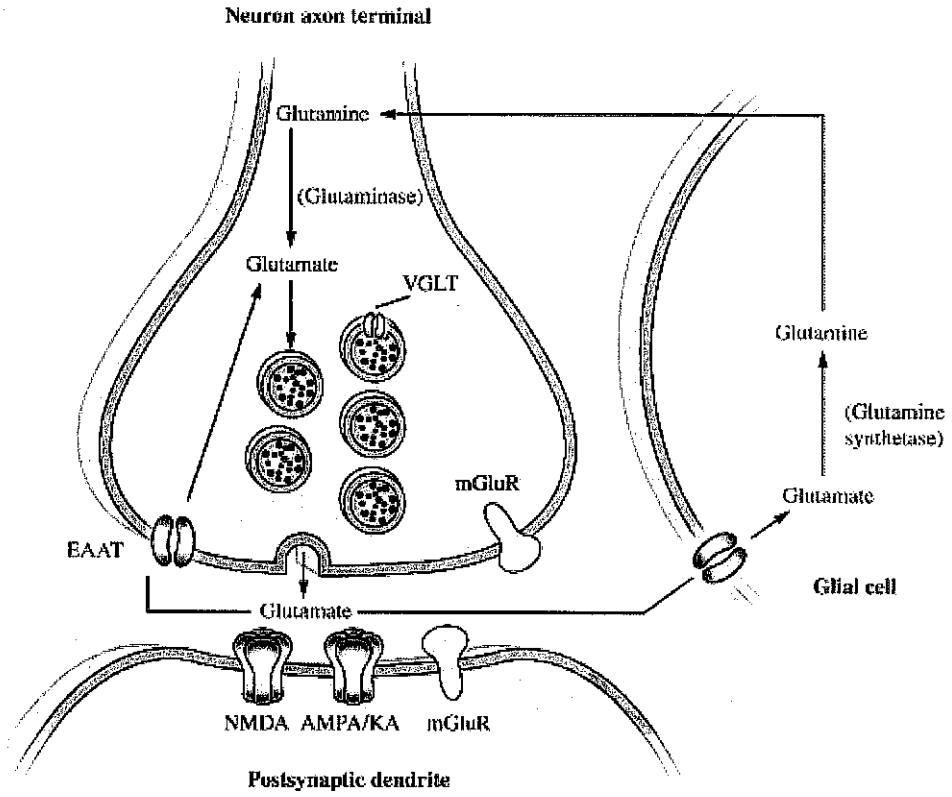

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FIGURE 2.18 Schematic of the glutamate synapse. Glutamate (Glu) is released into the synapse and recaptured by excitatory amino acid transporters (EAATs) located on the presynaptic terminal and on adjacent glial cells. Within the glial cells, glutamate is converted to glutamine by the enzyme *glutamine synthetase*. Glutamine diffuses back into neuronal terminals to replenish the Glu after conversion by the enzyme *glutaminase* and storage by vesicular glutamate transporters (VGLT). The "fast" (ionotropic) receptors, NMDA, AMPA, and kainate, are shown on the postsynaptic membrane; the "slow" (metabotropic, mGluR) receptors are shown on both the pre- and postsynaptic membranes.

Glutamate receptors consist of two families, the *ionotropic* receptors (which respond quickly) that include NMDA and non-NMDA receptors (AMPA and kainate receptors) and *metabotropic receptors* (which respond more slowly). Metabotropic glutamate receptors (abbreviated as mGluRs) consist of eight members arranged into three groups (receptor classification is discussed more fully in Chapter 3). In the adult human brain, NMDA and AMPA receptors are colocalized in about 70 percent of their synapses. These receptors mediate rapid excitation of postsynaptic neurons, with especially high concentrations in the cerebral cortex, hippocampus, basal ganglia, septum, and amygdala.

NMDA receptors (Figure 2.19) have some unusual characteristics. First, in addition to glutamate, another amino acid, either glycine or serine, also needs to be

addition to glutamate, another amino acid, either glycine or serine, also needs to be present for the receptor to be activated. Second, in order for NMDA receptors to be activated, they not only need to be stimulated by glutamate, but they also need to be sufficiently stimulated electrically. The reason for this is that the NMDA ion channel is normally blocked by magnesium ions (Mg^{2+}). Glutamate alone is not able to activate the receptor because of this block. However, when the neuronal membrane is also electrically stimulated, that is, depolarized (by the activation of AMPA or kainate receptors on the same postsynaptic neuron), the Mg^{2+} blockade of the ion channel is relieved. Then the NMDA receptor channel opens and permits the entry of both sodium and calcium ions, which further increases neuronal excitation. The NMDA receptor ion channel also has a binding site for phencyclidine (PCP) and ketamine (two psychedelic drugs discussed in Chapter 8). These two drugs also block the NMDA receptor (see Chapter 3) and therefore prevent glutamate-induced neuronal activation.

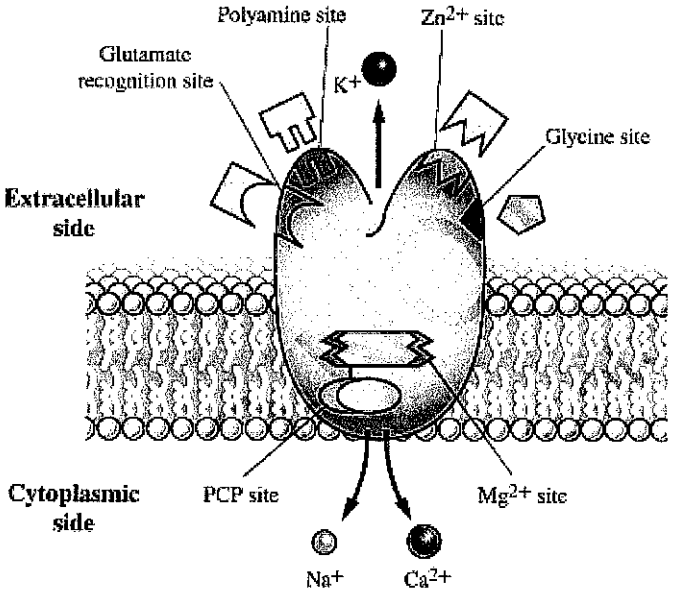

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FIGURE 2.19 Schematic drawing of the NMDA (*N*-methyl-D-aspartate) receptor (PCP is discussed in Chapter 8).

NMDA receptors play a critical role in regulating synaptic plasticity. Activation of these receptors is responsible for basal excitatory synaptic transmission and many forms of neurophysiological mechanisms that are thought to underlie learning and memory. Because these receptors are involved in cognitive processes, they are potential targets for therapies for Alzheimer's and other dementias. In 2004, memantine, the first anti-Alzheimer's drug that acts through a glutamatergic mechanism, became available for clinical use (see Chapter 16).

mechanism, became available for clinical use (see Chapter 16).

Although a normal amount of NMDA activity plays an important role in neuronal "health," excessive glutamatergic signaling is also involved in neuronal toxicity, a phenomenon by which nerve cells are damaged. Too much glutamate can lead to neuronal destruction through overactivity of NMDA receptors, which allows high amounts of calcium ions to enter the neuron (see Figure 2.19). Excess calcium activates enzymes, which then cause damage to cell structures and to DNA. For example, ethanol (see Chapter 5) reduces glutamate activity and alcohol withdrawal markedly increases glutamate release from neurons. Traumatic head injury also results in massive release of glutamate and attempts to provide "brain protection" after head injury is aimed at preventing glutamatergic overactivity. Anoxia (oxygen deficiency), hypoglycemia, and epilepsy are other glutamate-releasing events that can lead to neuronal damage. Research is also focusing on the possibility of glutamate dysfunction in the pathogenesis of schizophrenia, especially the negative symptoms and the cognitive dysfunction associated with the disorder (see Chapter 11).

Gamma Aminobutyric Acid

Gamma aminobutyric acid (GABA), the universal inhibitory transmitter, is found in high concentrations in the brain and spinal cord. Two different types of GABA receptors are categorized as $GABA_A$ and $GABA_B$ (Figure 2.20). *$GABA_A$ receptors* are fast receptors. Activation of this receptor by GABA opens an ion channel and leads to an influx of chloride into the cell, hyperpolarizing the cell and reducing its excitability. Barbiturate and benzodiazepine binding to this receptor facilitates the action of GABA (see Chapter 13), which is responsible for the anxiolytic, amnestic, and anesthetic effects of these sedative drugs. $GABA_A$ receptors are found in high density in the cerebral cortex, hippocampus, and cerebellum.

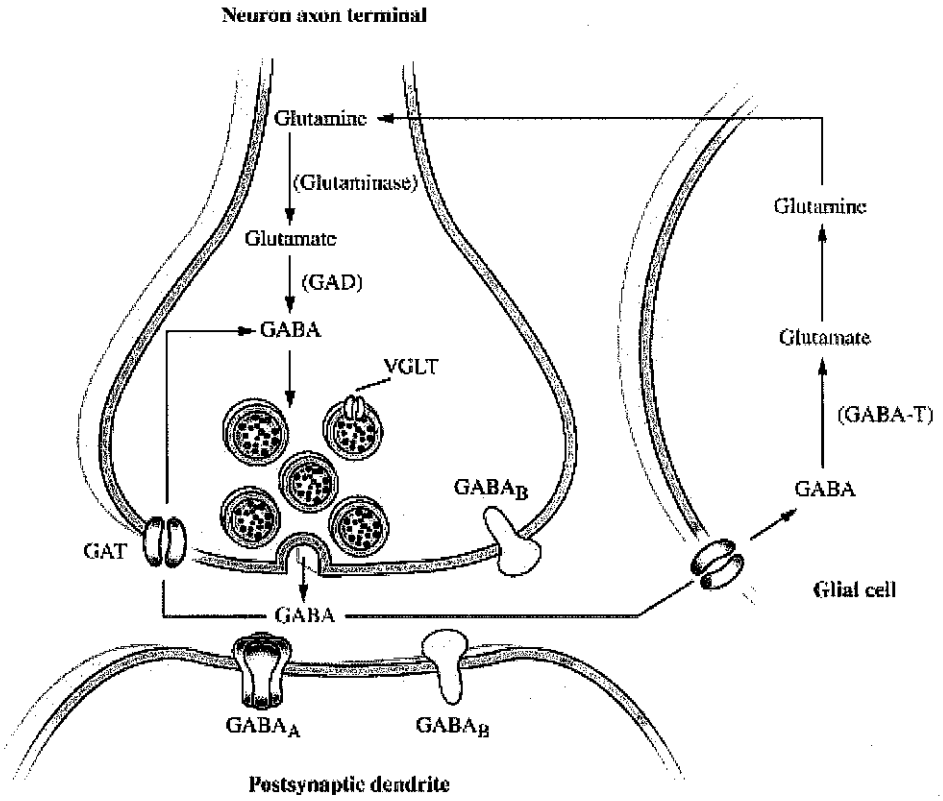

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FIGURE 2.20 Schematic of the GABA synapse. $GABA_A$ receptors are fast (ionotropic; Chapter 3) receptors and found on the postsynaptic membrane. $GABA_B$ receptors are metabotropic and found on both pre- and postsynaptic membranes. GAT is the GABA transporter; GAD is glutamic acid decarboxylase, which converts L-glutamic acid to GABA; GABA-T is the enzyme transaminase, which metabolizes GABA.

Numerous sub-subtypes of the $GABA_A$ receptor occur, allowing for the development of a variety of agonists and antagonists (see Chapter 13). Such drugs might be novel antianxiety agents, anticonvulsants, or cognitive enhancers.

$GABA_B$ receptors are slow-response receptors. Activation of $GABA_B$ receptors in the amygdala is associated with the membrane-stabilizing, antiaggressive properties of valproic acid, a drug widely used to treat bipolar disorder (see Chapter 14).

Peptide Neurotransmitters