

Chapter 16

Anesthetic Agents: General and Local Anesthetics

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Drugs Covered in This Chapter

INHALED GENERAL ANESTHETICS

- Ether
- Halothane
- Desflurane
- Enflurane
- Isoflurane
- Methoxyflurane
- Sevoflurane
- Nitrous oxide

INTRAVENOUS GENERAL ANESTHETICS

- Etomidate
- Ketamine

- Propofol
- Fospropofol
- Thiopental

LOCAL ANESTHETICS

- Articaine
- Benzocaine
- Bupivacaine
- Chloroprocaine
- Cocaine
- Dibucaine
- Dyclonine
- Mepivacaine

- Levobupivacaine
- Lidocaine
- Prilocaine
- Procaine
- Ropivacaine
- Tetracaine

Abbreviations

BTX, batrachotoxin

CNS, central nervous system

COCl₂, phosgene

EEG, electroencephalograph

EMLA, Eutectic Mixture of a Local Anesthetic

GABA, γ -aminobutyric acid

HBr, hydrobromic acid

HCl, hydrochloric acid

MAC, minimum alveolar concentration

Na/K-ATPase, sodium-potassium adenosine triphosphatase

NO, nitric oxide

NMDA, *N*-methyl-D-aspartate

PABA, *p*-aminobenzoic acid

PCP, phencyclidine

STX, saxitoxin

TTX, tetrodotoxin



SCENARIO

Paul Arpino, R.Ph.

CDL is a 70-year-old obese man scheduled for carpal tunnel surgery. A review of his medical file indicates a history of obstructive sleep apnea and benign prostatic hypertrophy (BPH). CDL sleeps with a continuous positive pressure airway device and his BPH is treated with tamsulosin, 0.4 mg daily. Given that patients with sleep apnea are at high risk for respiratory depression, the clinical team decides that a peripheral nerve block would be a better alternative to both neuraxial and general anesthesia.

During the preoperative assessment before the scheduled day of surgery, the team discovers that CDL has an undefined allergy to procaine (Novocain) and that he experienced severe blistering after a dental procedure many years ago and was told he cannot receive “drugs like Novocain again.”

(The reader is directed to the clinical solution and chemical analysis of this case at the end of the chapter).

INTRODUCTION

Anesthesia, defined as a loss of sensation with or without loss of consciousness, can be effectively achieved with a wide range of drugs with very diverse chemical structures. The list of such compounds includes not only the classic anesthetic agents, such as the general and local anesthetics, but also many central nervous system (CNS) depressants, such as analgesics, sedative/hypnotics (barbiturates and benzodiazepines), anticonvulsants, and skeletal muscle relaxants. Although various mechanisms of action are attributed to these agents, ultimately they all produce their anesthetic actions by interfering with conduction in sensory neurons and sometimes also motor neurons. Many of these agents are routinely used today in clinical practice to facilitate surgical and medical procedures. This chapter will focus on those agents typically classified as “general” and “local” anesthetics.

GENERAL ANESTHETICS

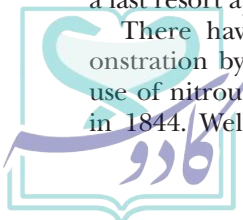
Prior to the mid-1800s, pain-producing surgical and dental procedures typically were undertaken without the aid of effective anesthetic agents. Chemical methods available at the time included intoxication with ethanol, hashish (cannabis), or opium, whereas physical methods included packing a limb in ice, creating ischemic conditions with tourniquets, inducing unconsciousness by a blow to the head, or the most common technique, employing strong-armed assistants to hold down the helpless patient during the entire painful surgical procedure. Additionally, at this time, many practicing physicians had been erroneously taught that pain was a requirement for effective healing; therefore, the observation of a patient in terrible pain was viewed as part of the normal healing process. These factors, along with the lack of knowledge regarding aseptic techniques or the availability of suitable infection-fighting agents, made surgical procedures a last resort approach to treating disease.

There have been many accounts of the first demonstration by the Hartford dentist Horace Wells of the use of nitrous oxide as a general anesthetic for surgery in 1844. Wells first observed the anesthetic actions of

nitrous oxide at a public demonstration of “laughing gas.” One of the volunteers, a pharmacy clerk named Samuel Cooley, injured his leg while under the influence of this gas and appeared to experience no pain. The next day, Wells inhaled the gas himself and, with the aid of a colleague, had one of his own teeth extracted without any sensation of pain. Wells then began routinely using nitrous oxide for dental procedures in his own practice. In 1845, he attempted to demonstrate the anesthetic effects of nitrous oxide at the Massachusetts General Hospital in Boston. This demonstration was considered to be a failure, however, because the patient cried out in the middle of the procedure. Following this unfortunate incident, the use of nitrous oxide was minimal until it resurfaced in dental practice during the mid-1860s, when it was combined with oxygen and made available in steel cylinders. This gas is still commonly used today, especially in combination with other anesthetic and analgesic agents.

The general anesthetic that gained greatest popularity shortly after the failed demonstration of Wells was diethyl ether. William Morton, a Boston dentist, was familiar at the time with the use of nitrous oxide by Wells. He also had heard of the interesting effects of diethyl ether and began to experiment on animals and himself with this volatile liquid. In 1846, he was allowed an opportunity to demonstrate the anesthetic actions of diethyl ether at, again, the Massachusetts General Hospital. In the famed “Ether Dome,” which still stands today, Morton administered diethyl ether with a specially designed delivery device to the nervous patient, and the surgical procedure was performed without apparent pain. Following this demonstration, word of its success spread quickly, and soon, dental and medical practices throughout the United States and Europe were employing diethyl ether as a general anesthetic agent. Today, diethyl ether is no longer used in procedures because of its toxicity and dangerous physical properties (e.g., it is flammable and explosive!).

Other general anesthetic agents that enjoyed early popularity were chloroform and cyclopropane. Chloroform vapor depresses the CNS of a patient, allowing a doctor to perform various otherwise painful surgical procedures.



CLINICAL SIGNIFICANCE



Anesthetics are a structurally diverse class of medications that enable clinicians to perform surgery and other noxious procedures.

Understanding the essential components of the anesthetic state (i.e., immobilization, analgesia, and amnesia) as well as the medicinal chemistry of the various anesthetic agents allows the clinician to optimize therapy to meet patient specific needs. The patient undergoing a minimally invasive ambulatory surgical procedure may only require a local anesthetic with adjunctive pain control. Alternatively, patients undergoing a major surgical procedure may require general anesthesia with several different classes of anesthetics as well as several adjunctive medications to counteract deleterious emergence reactions related to the anesthetics. In both cases, a thorough understanding of the basic chemical properties of the drugs and their respective mechanisms of action will prove invaluable to making appropriate clinical decisions.

The practice of anesthesia is typically not considered to be therapeutic; therefore, the practice as well as the development

of new agents is aimed at reducing adverse reactions, maintaining optimal physiologic conditions during procedures, and minimizing postoperative complications related to the procedure itself. The study of medicinal chemistry gives us hope for future treatment options, and knowledge of structure-activity relationships fosters the development of new medications and administration techniques. New generations of drugs are being created by modifying the structures of existing compounds to improve the side effect and pharmacokinetic profiles. Clinicians will have to stay up to date with new developments in anesthesia practices, the molecular actions of anesthetics, and the pharmacokinetic properties of the drugs to provide the best therapeutic outcomes for patients.

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In 1847, the Scottish obstetrician James Young Simpson first used chloroform for general anesthesia during childbirth. The use of chloroform during surgery expanded rapidly thereafter in Europe. In the United States, chloroform replaced diethyl ether as an anesthetic at the beginning of the 20th century; however, it was quickly abandoned due to its cardio and CNS toxicity. Cyclopropane is a hydrocarbon with anesthetic properties like diethyl ether, except it is also explosive and is no longer used. As described later in this chapter, the inhalational general anesthetic agents used today are typically hydrocarbons and halogenated ethers (Cl, Br, or F); nitrous oxide is the exception. Table 16.1 lists the characteristics of the “ideal” general anesthetic agent. Unfortunately, the agent that fulfills all these characteristics is currently unknown.

Stages of General Anesthesia

The ideal general anesthetic state is characterized by a loss of all sensations and includes analgesia and muscle relaxation. Neuronal depression in specific areas of the CNS is believed to be largely responsible for such an anesthetic state. The areas involved include many cortical regions that are represented by excitatory pyramidal cells and inhibitory/excitatory stellate cells. Excitation of the pyramidal cells helps to maintain consciousness, whereas the degree of inhibition or excitation of stellate cells determines the overall activity level of the pyramidal cells with which they synapse. As the concentration of the anesthetic agent increases in the brain, the degree of overall neuronal depression also increases, resulting in progressively deeper stages of anesthesia. Based on observations using diethyl ether, Guedel in 1920 originally described this progression as four distinct stages,

and Gillespie subsequently further subdivided these stages (Fig. 16.1), as described in the following sections.

Stage 1: Analgesia

Characterized by a mild depression of higher cortical neurons, this stage is suitable for minor surgical procedures that do not require significant neuromuscular relaxation. Depression of thalamic centers probably accounts for the observed analgesia, because many of the neuronal systems that mediate pain sensation traverse through this anatomic area. Some general anesthetic agents do not possess significant analgesic activity, but they all produce a loss of consciousness that, in turn, can produce some degree of insensitivity to painful stimuli.

TABLE 16.1 Characteristics of the Ideal General Anesthetic Agent

Rapid and pleasant induction of surgical anesthesia
Rapid and pleasant withdrawal from surgical anesthesia
Adequate relaxation of skeletal muscles
Potent enough to permit adequate oxygen supply in mixture
Wide margin of safety
Nontoxic
Absence of adverse effects
Nonflammable/nonexplosive
Chemically compatible with anesthetic devices
Nonreactive
Inexpensive

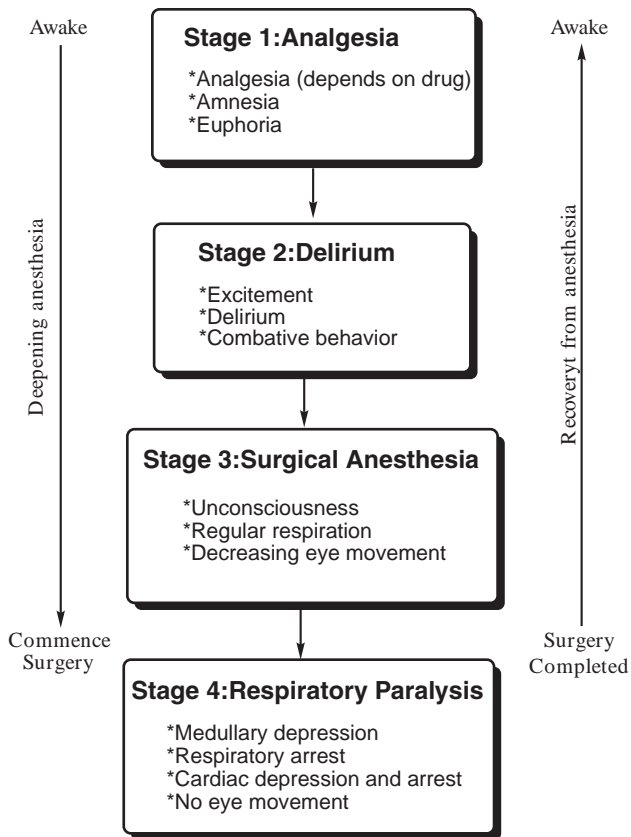


FIGURE 16.1 Stages of general anesthesia.

Stage 2: Delirium

As depression of inhibitory neurons in the CNS progresses, especially in the reticular formation (a network of neurons in the brainstem), a resultant excitation of cortical motor neurons leads to significant involuntary muscle activity, such as urination, delirium, uncontrolled skeletal muscular movements, and increased heart rate, blood pressure, and respiration. These paradoxical responses are caused by suppression of inhibitory neurons that normally function to closely regulate such neuronal activity. Ideally, an anesthetic agent should produce little or no excitatory phase. Together, stages 1 and 2 comprise the induction period, which ideally should be of short duration.

Stage 3: Surgical Anesthesia

This stage is divided into four planes characterized by increasing CNS depression: first, loss of spinal reflexes; second, decreased skeletal muscle reflexes; third, paralysis of intercostal muscles; and fourth, loss of most muscle tone. Stage 3 is also characterized by regular breathing, a loss of many reflexes, and roving eyeball movements.

Stage 4: Respiratory Paralysis

Characterized by respiratory and vasomotor paralysis, this stage represents an overdose or toxic level that should be avoided. Normally, this stage is never reached, because the anesthesiologist is careful to monitor abdominal

respiration to prevent apnea, blood pressure to prevent hypotension, and heart rate to prevent asystole (a state of no cardiac electrical activity).

Modern General Anesthetic Agents

Although these stages have been described for diethyl ether, an anesthetic agent no longer used today. Some of today's clinically useful general anesthetic agents fail to follow this described pattern of anesthetic progression. Some attempts have been made to correlate changes in the electroencephalograph (EEG) with the depth of anesthesia. Most of these studies, however, have failed to yield a reliable predictor for anesthesiologists to use. Additionally, concomitant drugs used as preanesthetic agents can alter the EEG while not altering the depth of anesthesia. Rather than describing specific stages or using EEG patterns, a number of useful signs that more accurately reflect the depth of anesthesia for most of the anesthetic agents are currently used. When during the initial period of anesthetic administration a patient has irregular respiratory depth and rate, is still swallowing, and blinks the eyes when the eyelashes are touched, the desired surgical stage of anesthesia likely has not been reached. However, when a loss of the eyelash reflex occurs along with rhythmic breathing, however, a level of adequate surgical anesthesia has generally begun. If a patient at this stage exhibits elevations in blood pressure, increased respiration rate, or increased jaw tension when a surgical incision is attempted, the subject is considered to be "light" and typically requires additional anesthesia to facilitate further surgical manipulations. These responses decrease further—until they are abolished—as the depth of anesthesia progresses. By monitoring reflexes, blood pressure, and respiration rate and depth, today's anesthesiologist is capable of effectively maintaining an appropriate depth of surgical anesthesia without producing unwanted medullary depression.

Pharmacokinetic Principles of Volatile Anesthetics

The production and maintenance of the anesthetic state is believed by most to be dependent on the concentration, or partial pressure, of the anesthetic agent in yet unknown areas of the brain. Obviously, the concentration of the anesthetic agent in the gas mixture administered, as well as the rate and depth of respiration of the patient, will influence the rate of anesthesia induction. The rate at which delivery of anesthetic agents to these sites occurs is dependent on their physicochemical properties, particularly their solubility in lipid and blood (Fig. 16.2).

Administration of Volatile Anesthetics

The administration of gaseous or volatile liquid anesthetics involves a number of sophisticated devices that have been refined over the years to aid the anesthesiologist in carefully controlling the amount of anesthetic delivered to the patient while minimizing the exposure of the



FIGURE 16.2 Dynamic equilibria existing during the state of anesthesia.

surgical personnel to these agents. Early systems used a gauze pad in a mask placed over the nose and mouth of the patient. The anesthesiologist would then put drops of the volatile anesthetic on the gauze pad, and as the patient breathed, the anesthetic was delivered to the lungs. This procedure was somewhat effective, but it allowed little or no control over the amount of anesthetic and oxygen delivered to the patient. Thus, the anesthetic agent not inhaled was allowed to evaporate into the surrounding area in the surgical suite and posed a significant risk to the surgical personnel. Today, flowmeters, vaporizers, and absorber devices are routinely available, allowing precise determination and control of the amount of volatile anesthetic, oxygen, and carbon dioxide administered while preventing significant exposure to workers. Typically, oxygen is bubbled through a volatile anesthetic liquid, and the resultant gas mixture is delivered to the patient for continual inhalation. Many of these devices are described in greater detail elsewhere (1).

The inhaled anesthetic concentration is controlled by the anesthesiologist, who can either increase or decrease this concentration depending on the observed depth of anesthesia. Eventually, with continued administration, the concentration of anesthetic in the bronchiolar alveoli reaches equilibrium with that in the inspired gas mixture (Fig. 16.2). Transfer from the alveolar space to the blood proceeds quickly, and depending on the concentrations of anesthetic used and its physiochemical characteristics, equilibrium with the arterial blood is achieved. However, before appreciable amounts of anesthetic agent dissolved in the blood will enter the brain, the blood must be saturated with the anesthetic. Therefore, anesthetics that are

more soluble in the blood (have a low blood/gas partition coefficient, Fig. 16.2) will require a longer time to achieve saturation of the blood–brain compartment. In such cases, the time for induction will be prolonged. On the other hand, an anesthetic that is poorly soluble in blood (has a high blood/gas partition coefficient, Fig. 16.2) will quickly saturate the blood compartment and then rapidly enter the tissues to produce a short induction period. Similarly, agents with high blood/gas partition coefficients will require a longer time for recovery from anesthesia. The solubility of an agent in the blood is usually expressed as the blood/gas partition coefficient, which is the ratio of the concentration of anesthetic in blood to that in the gas phase at equilibrium (Table 16.2). These values correspond well with the oil/gas partition coefficient, which is easier to determine experimentally. The blood/gas partition coefficient can be very high (e.g., 12) for soluble agents, such as methoxyflurane, and extremely low (e.g., 0.47) for poorly soluble agents, such as nitrous oxide.

The solubility of the anesthetic in tissue is expressed as the tissue/blood partition coefficient. Because the concentration of the anesthetic in the brain is probably of most interest, the brain/blood partition coefficient is more useful. Because the solubility of the anesthetic in lean tissues is essentially equal to that in blood, the tissue/blood or brain/blood partition coefficient is typically close to a value of 1. In fatty tissues, however, the partition coefficient can be much larger due to lipid solubility. The rate of blood flow to a particular organ will also influence the rate at which anesthetics reach their sites of action. The brain, liver, and kidneys have relatively high

TABLE 16.2 Partition Coefficients, MACs, and Metabolism of Some General Anesthetics

Anesthetics	Partition Coefficients at 37°C			MAC (vol %) ^a		% Metabolism
	Oil/Gas	Blood/Gas	Without N ₂ O	With N ₂ O (%)	MAC-Awake (Vol %)	
Methoxyflurane	970	12	0.16	0.07 (56)	—	50
Halothane	224	2.3	0.77	0.29 (66)	0.4	20
Enflurane	99	1.9	91.7	0.60 (70)	0.4	2.4
Isoflurane	97	1.4	1.15	0.50 (70)	0.4	0.17
Sevoflurane (2)	53	0.60	1.71	0.66 (64)	0.6	4–6
Desflurane (3)	19	0.42	6.0	2.83 (60)	2.4	0.02
Nitrous oxide	1.4	0.47	104	—	60	None

^aMAC = minimum alveolar concentration, expressed as volume %, that is required to produce immobility in respect to a standard surgical incision in 50% of middle-aged humans.

blood flows, whereas skeletal muscle at rest and fat tissues have relatively poor blood flows and would be expected to accumulate less of the anesthetic agent.

Reversal of the anesthetic state and recovery requires a reduction in the concentration of the anesthetic in the brain. This is achieved by stopping the delivery of the anesthetic through the lungs. As the patient continues to breathe, the anesthetic is continually removed, which favors diffusion from the brain to the blood, to the alveoli, and finally, to the expired air. The rate at which this occurs generally parallels that of induction, because the solubility of an agent in the brain and in the blood determines how quickly these compartments will return to a preanesthetic state. The main route of elimination is via the expired air, which can be mostly captured by gas-scavenging devices with absorbers, but some metabolism of these agents does take place (discussed below).

Minimum Alveolar Concentration

The minimum alveolar concentration (MAC) is defined as the concentration at 1 atmosphere of anesthetic in the alveoli that is required to produce immobility in 50% of adult patients subjected to a standard surgical incision. A further increase to 1.3 MAC will frequently cause immobility in 99% of patients. At equilibrium, the concentration (or partial pressure) of an anesthetic in the alveoli is equal to that in the brain, and it is this concentration in the brain that most closely reflects the concentration at the site responsible for the anesthetic actions. Thus, the MAC is often used as a measure of the potency of individual anesthetic agents. The MAC of many of the volatile and gaseous anesthetics in use today is shown in Table 16.2.

When anesthetic agents are used in combination, the MACs for inhaled anesthetics are simply additive. For instance, the anesthetic depth achieved with 0.5 MAC of enflurane plus 0.5 MAC of nitrous oxide is equivalent to that produced by 1.0 MAC of either agent alone. The combination of two anesthetics is a very common practice, because this technique allows for a reduction in the patient exposure to any one of the individual agents, thereby decreasing the likelihood of adverse reactions.

Many factors influence the MAC via a number of different mechanisms (Table 16.3). Factors that have been shown to increase the MAC for many volatile anesthetics include elevated catecholamines in the CNS following pharmacologic treatments, hypernatremia, and hyperthermia. Factors known to decrease MAC include ethanol ingestion, clonidine, lithium, lidocaine, centrally administered opioids, and drugs that decrease central catecholamine levels. Additionally, hyponatremia, hypotension, hypothermia, hypoxia, increasing age, and pregnancy have also been shown to decrease MAC. Plasma potassium, hypertension, gender, and the duration of anesthesia typically generally have minimal to no effect on the MAC (2).

Another term, the “MAC-Awake,” is used to describe the concentration of anesthetic at which appropriate

TABLE 16.3 Factors That May Alter MAC

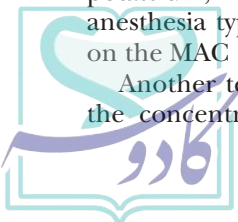
Increase MAC	Increased catecholamine levels in CNS Hypernatremia Hyperthermia	
Decrease MAC	Decreased catecholamine levels in CNS Alcohol Ingestion Clonidine Lidocaine Lithium Opioids	Hyponatremia Hypotension Hypothermia Hypoxia Increased age Pregnancy
No effect on MAC	Plasma potassium Gender Hypertension Duration of anesthesia	

responses to verbal commands are lost in 50% of the patients tested. At this concentration, amnesia and a loss of awareness are evident, and the patient is said to be in a state of hypnosis. The MAC-Awake occurs at concentrations significantly lower (e.g., 50% to 75% lower) than those required for surgical anesthesia.

Theories About the Mechanisms of Anesthesia

Meyer-Overton Theory

In the early 1900s, Hans Meyer and Charles Overton suggested that the potency of a substance as an anesthetic was directly related to its lipid solubility, or oil/gas partition coefficient (Table 16.2) (3–5). This has commonly been referred to as the “unitary theory of anesthesia.” They used olive oil, octanol, and other “membrane-like” lipids to determine the lipid solubility of the agents available at that time. Compounds with high lipid solubility required lower concentrations (i.e., lower MAC) to produce anesthesia. It was later postulated that the interaction of the anesthetic molecules with a hydrophobic portion of the nerve membrane caused a distortion of the nerve membrane near the channels that conducted Na^+ , those that mediated the fast action potentials and neuronal cell firing. The presence of this critical volume of anesthetic dissolved within the membrane caused the membrane to “bloat” and cause a “squeezing in” on the Na^+ channel to interfere with Na^+ conductance and normal neuronal depolarization. In support of this theory, it was found that at high pressures (40 to 100 atmospheres), the anesthetic actions of many of these agents could be partially reversed, presumably by compressing membranes back to their original conformation. Arguing against this theory, however, is the finding that not all highly lipid-soluble substances are capable of producing anesthesia. Additionally, more recent work involving protein–drug interactions has seriously challenged this theory. Today, more than 150 years after the first demonstration of the use of a volatile anesthetic agent, most theories about the mechanisms of anesthesia suggest that multiple selective



lipid–protein membrane interactions, involving numerous receptor types, are responsible for the anesthesia produced and that no reason exists to believe that all anesthetic agents need to produce their effects via identical actions. Thus, a single molecular target for anesthetic actions is no longer required (6).

Stereochemical Aspects

The volatile anesthetics isoflurane, desflurane, enflurane, and halothane each contain an asymmetric carbon and, thus, can exist as (+)- or (–)-enantiomers. Although all of the commercially available preparations are racemates, some researchers have been able to determine the anesthetic properties of individual enantiomers. The (+)-enantiomer of isoflurane is at least 50% more potent as an anesthetic in the rat than is the (–)-enantiomer (7). In that study, the MAC values were 1.06% and 1.62% for the (+)- and (–)-enantiomers, respectively. In another study, however, the potency of the individual isoflurane enantiomers to depress myocardial activity was not found to be different, suggesting possible involvement of mechanisms dissimilar from those responsible for producing anesthesia (8). These findings argue against the original and simple lipid-solubility theory of anesthesia, and they support a more complex mechanism, probably likely involvement of proteins in the form of receptor–anesthetic interactions (9).

Ion Channel and Protein Receptor Hypotheses

More recently, investigators have determined the effects of anesthetics on a number of protein receptors within the CNS. Features that support the likelihood of an interaction with a protein include 1) the steep dose–response

curves observed, 2) the stereochemical requirements of various anesthetics, 3) the finding that increasing the molecular weight and corresponding lipid solubility of an anesthetic can actually decrease or abolish anesthetic activity, and 4) the finding that specific ion channels and neurotransmitter receptor systems are required for most of the observed effects of the anesthetics. What appears to be emerging as a central theme for the mechanism of action of general anesthetics involves the interaction of the anesthetics with receptors that allosterically modulate the activity of ion channels (e.g., chloride and potassium) or with the ion channel directly (e.g., sodium). Many other mechanisms are also emerging to help explain the mechanisms of action of the general anesthetics.

CHLORIDE CHANNEL The ion channel that has received the most investigative attention is that for chloride (Fig. 16.3). Both the γ -aminobutyric acid_A (GABA_A) and the glycine_A (strychnine-sensitive) receptors are ligand-gated ion channels and linked to chloride channels that normally mediate inhibitory responses within the CNS. Halothane, isoflurane, and other volatile anesthetics are capable of inhibiting the synaptic destruction of GABA, thereby increasing the GABAergic neurotransmission, which typically is inhibitory in nature (10). Studies have also demonstrated the ability of these anesthetics to enhance the binding of GABA or other allosteric modulators within the GABA receptor complex (11). In one such study, (+)-isoflurane was significantly more potent than the (–)-enantiomer at enhancing GABAergic function (12). The volatile anesthetics, and many of the intravenous general anesthetic agents, bind to discrete cavities within the GABA_A

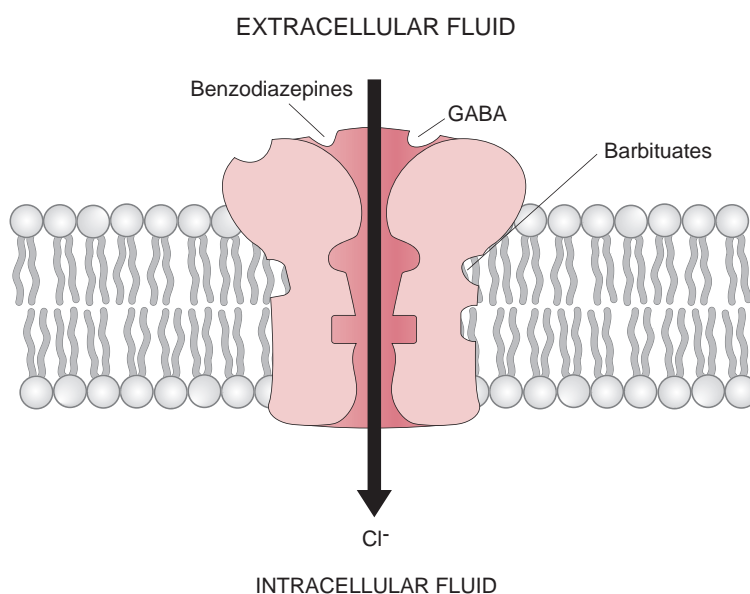


FIGURE 16.3 The GABA_A receptor controls the chloride ion channel. GABA binds to its receptor, opening the chloride ion channel and resulting in hyperpolarization of the neuron. Benzodiazepines and barbiturates can produce anesthesia by allosterically enhancing GABA opening of chloride channels, which are located at inhibitory synapses on pyramidal cells.

receptor complex to enhance GABA neurotransmission (13,14). Studies using mutant chimeric GABA_A receptors have identified a specific binding site for general anesthetics located between transmembrane segments 2 and 3 (15). At therapeutic concentrations, just about all of the inhalational general anesthetics are capable of enhancing GABAergic function, whereas at considerably higher concentrations, many also can act directly as GABA mimetics (16). Recent studies have demonstrated an effect of these agents not only on the synaptic GABA_A receptor function that mediates phasic neuronal responses but also on those extrasynaptic GABA_A receptors that mediate tonic neuronal activity (17). Other specific anesthetic agents can alter GABA_A receptor function via different mechanisms. For instance, propofol, an intravenous general anesthetic, appears to slow the desensitization of the GABA_A receptor during bouts of rapid, repetitive activation at inhibitory synapses (18). Most of these agents also potentiate the actions of glycine, the other important inhibitory amino acid neurotransmitter (16). The combination of GABAergic and glycinergic potentiation by the general anesthetics probably accounts for the vast majority of the observed activity of the inhalational agents as well as that of the barbiturates.

SODIUM CHANNELS One channel that has received much attention regarding the mediation of drug-induced anesthetic actions is the ligand-gated Na⁺ channel within the

N-methyl-D-aspartate (NMDA) receptor complex. When activated by the excitatory amino acid neurotransmitter, glutamate, an increase in the conductance to Na⁺ occurs that promotes neuronal depolarization (Fig. 16.4) (19). Compounds known to stimulate NMDA receptors are typically capable of increasing alertness and of acting as convulsants, whereas pharmacologic agents that act as antagonists at this site are usually sedatives, anticonvulsants, and dissociative anesthetics (e.g., ketamine). Halothane has been demonstrated to specifically antagonize the glutamate-stimulated depolarization of neurons (20), whereas isoflurane has been shown to decrease glutamate release and enhance its removal from the synaptic cleft (21). Glutamate acting at NMDA and other non-NMDA receptors within the CNS is probably one of the most important excitatory inputs that supports consciousness. It is not surprising that the general anesthetics would act by altering neurotransmission in this system (22). Others have reported an interaction of general anesthetics with the neuronal nicotinic acetylcholine receptor-linked Na⁺ channel (23). Voltage-gated Na⁺ channels in small, nonmyelinated hippocampal axons also appear to be inhibited by general anesthetics, such as isoflurane (24).

POTASSIUM CHANNELS Potassium ion channels have also been suggested as a site for general anesthetic agents. Increasing K⁺ conductance normally functions to maintain the polarized state of neurons and to assist in the

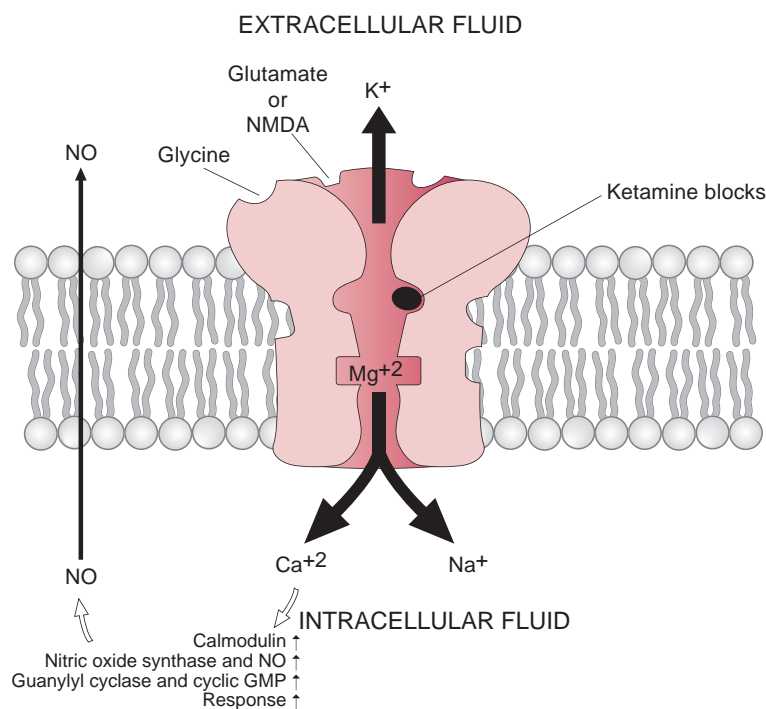
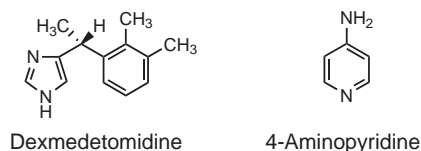


FIGURE 16.4 Glutamate or NMDA receptors in the CNS. Binding of agonists (glutamate or NMDA) opens the channel, allowing K⁺ to flow outward to extracellular fluid and sodium and calcium ions to flow into the nerve cells. Increased intracellular fluid calcium ion concentration triggers a cascade that produces a response and liberates the retrograde neuronal messenger nitric oxide (NO). Ketamine can produce anesthesia by blocking these NMDA-controlled channels, which are located at excitatory synapses on pyramidal cells (3). Glycine acts as a positive allosteric modulator at the NMDA receptor.

repolarization of neurons following their stimulation-induced depolarization (Fig. 16.5). Thus, enhancing the activity of certain K^+ channels would be expected to result in a decreased likelihood of neuronal excitation. A novel, anesthetic-sensitive K^+ current [$I_{K(an)}$] has been identified that is stereoselectively activated by isoflurane (25). Mice with a targeted deletion of the TREK-1 two-pore-domain K^+ channel show significantly reduced sensitivity to general anesthetics compared to wild-type controls (26). Additionally, certain α_2 -adrenoceptor agonists (e.g., dexmedetomidine) when injected produce an anesthetic state that is mediated by a G protein-coupled receptor that allosterically modulates K^+ channels. These responses can be antagonized by pertussis toxin and 4-aminopyridine, agents that inactivate G proteins and block K^+ channels, respectively, lending further support to the role of this ion channel (27). Similarly, G protein-mediated mechanisms appear to be involved with the action of morphine via the μ -opioid receptor (Fig. 16.5).



Halogenated Hydrocarbons and Ethers

Historical Aspects

ETHER The useful volatile anesthetics, with the exception of nitrous oxide, are halogenated hydrocarbons and ethers. Diethyl ether (Fig. 16.6), one of the first

agents to be introduced as a general anesthetic, has high potency with significant analgesic and neuromuscular relaxing effects. This agent is extremely flammable, and when mixed with air, oxygen, or nitrous oxide, is explosive. Induction with diethyl ether is very slow; significant time is spent progressing through the delirium stage. Irritation of the respiratory tract by diethyl ether can lead to excessive bronchial secretions, complicating adequate ventilation. In addition to its unpleasant induction and adverse effects, recovery is similarly prolonged and can be accompanied by vomiting. These pharmacologic and physical characteristics of diethyl ether have limited the utility of this anesthetic in humans.

SHORT-CHAIN HYDROCARBONS Many of the short-chain alkanes, alkenes, and alkynes are capable of producing an anesthetic state when administered to patients. Potency generally increases as chain length increases. However, because of their flammability and increased propensity to cause cardiovascular toxicity, these nonsubstituted hydrocarbons are not useful as anesthetic agents.

CHLOROFORM Another of the earlier anesthetic agents to be used was chloroform ($CHCl_3$). This halogenated hydrocarbon was first officially used in the United States in 1847; however, its toxicity seriously limited its utility. The addition of halogens to the hydrocarbon backbone increases potency and volatility, as well as decreases flammability. Similar effects are also observed with such substitutions on ethers. As an anesthetic agent, chloroform is very potent and possesses significant analgesic and neuromuscular

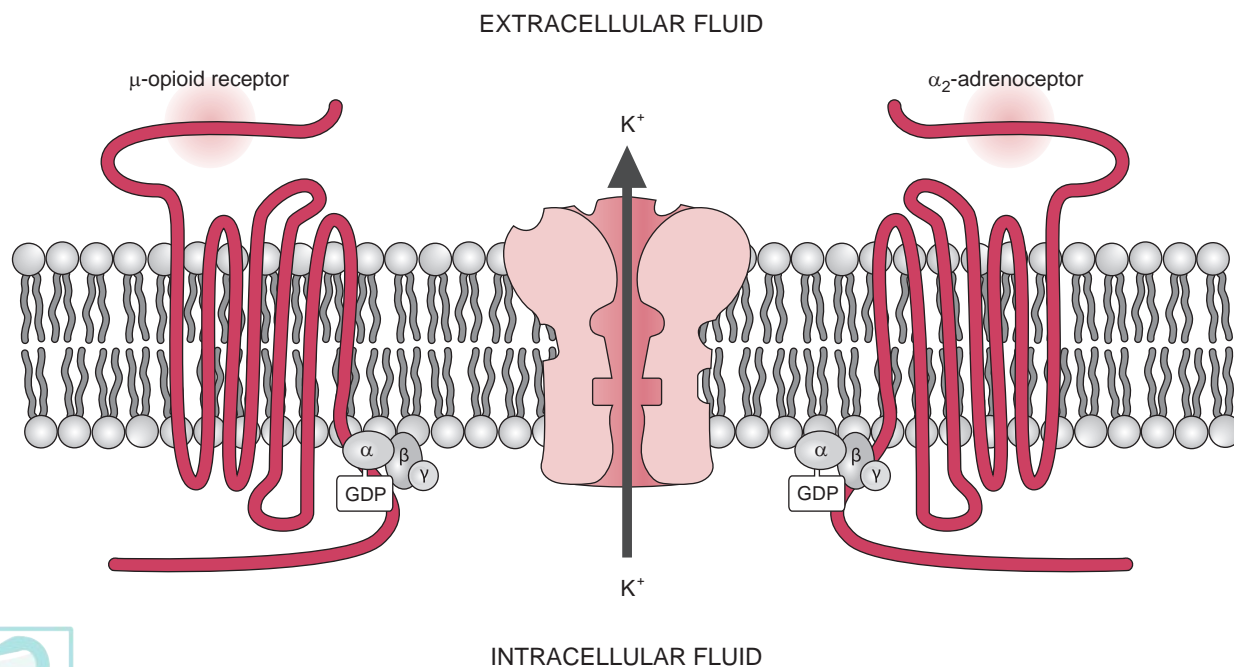


FIGURE 16.5 Morphine and α_2 -agonists activate their respective G proteins, which hyperpolarize neurons by lowering intracellular fluid K^+ ion concentration.

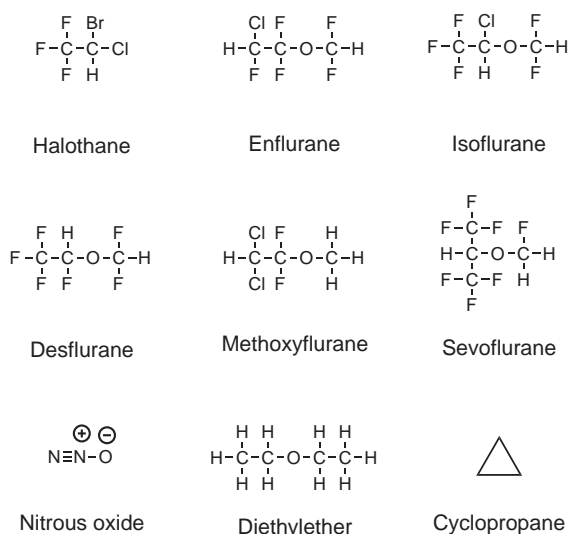


FIGURE 16.6 General anesthetics.

relaxing activity. Chloroform, a known carcinogen, has the disadvantage of being both hepatotoxic and nephrotoxic, in addition to producing adverse cardiovascular effects, such as arrhythmias and severe hypotension. As a result of these toxicities, chloroform has an unacceptable therapeutic index that prohibits its use in anesthesia. Two other halogenated compounds that found limited use in the mid-1900s included trichloroethylene and fluoro-xene. Neither of these agents is used today. Knowledge regarding the influence of the halogen substitutions on the potency and flammability of hydrocarbons and ethers, however, significantly contributed to our understanding of the structure–activity relationship of volatile anesthetics and the eventual design of substantially improved agents.

FLAMMABILITY The occurrence of fires in operating rooms is of great concern to all participants in the surgical procedure. Although the introduction of “nonflammable” agents, such as halothane, enflurane, and isoflurane, has substantially decreased this hazard, such fires still occur. Three essential ingredients are required for any combustion: 1) an ignition source (e.g., a laser), 2) a combustible material (e.g., gauze, drapes, or rubber tubes), and 3) an oxidizing agent (e.g., oxygen or nitrous oxide). Many substances are flammable in pure oxygen, nitrous oxide, or mixtures, but not air. Certain substances are flammable in nitrous oxide at concentrations that are too low to permit ignition in pure oxygen (28). The concentrations required for combustion, as indicated in Table 16.4, are higher than those generally encountered, except possibly during induction.

Clinically Useful Inhalation Agents

Fluorinated Hydrocarbons

The structure, physical properties and partition coefficients of the volatile anesthetics are given in Tables 16.2 and 16.5, respectively. Toxic degradation products

TABLE 16.4 Relative Flammability of “Nonflammable” Anesthetics

	Halothane (%)	Enflurane (%)	Isoflurane (%)
MFC of agent in 30% O ₂ with remaining atmosphere N ₂ O	4.75	5.75	7.0
MAC of agent given in above atmosphere	0.28	0.65	0.46
MAC in humans in the absence of N ₂ O	0.75	.68	1.15
MFC/MAC in N ₂ O	17	8.9	15.2

MFC, minimum flammable concentration; MAC, minimum effective alveolar concentration

are formed by reaction of the anesthetic agent with the basic substances such as soda lime, used as carbon dioxide absorbents during anesthesia. This reaction results in the conversion of halothane to 2-bromo-2-chloro-1,1-difluoroethylene, sevoflurane to 2-(fluoromethoxy)-1,1,3,3,3-pentafluoro-1-propene (Compound A), and desflurane, isoflurane, and enflurane to carbon monoxide. Compound A forms a glutathione S-conjugate, which undergoes hydrolysis to cysteine S-conjugates and bioactivation of the cysteine S-conjugates by renal cysteine conjugate β-lyase to give nephrotoxic metabolites.

HALOTHANE Halothane (Fig. 16.6) was introduced into medical practice in the United States in 1956 as a non-flammable, nonexplosive, halogenated volatile anesthetic that is usually mixed with air or oxygen. The presence of

TABLE 16.5 Physicochemical Properties of Clinically Useful Volatile Anesthetics

Generic Name (Trade Name) and Structure	Boiling Point (°C)	Chemically Stable ^a
Desflurane (Suprane) F ₂ HC–O–CHF–CF ₃	23.5	Yes
Enflurane (Ethrane) F ₂ HC–O–CF ₂ –CHFCl	56.5	Yes
Halothane (Fluothane) F ₂ C–CHBrCl	50.2	No
Isoflurane (Forane) F ₂ HC–O–CHCl–CF ₃	48.5	Yes
Methoxyflurane (Penthrane) H ₂ C–O–CF ₂ –CHCl ₂	104.7	No
Nitrous oxide N ₂ O	–*8.0	Yes
Sevoflurane (Ultane) (CF ₃) ₂ CH–O–CH ₂ F	58.5	No

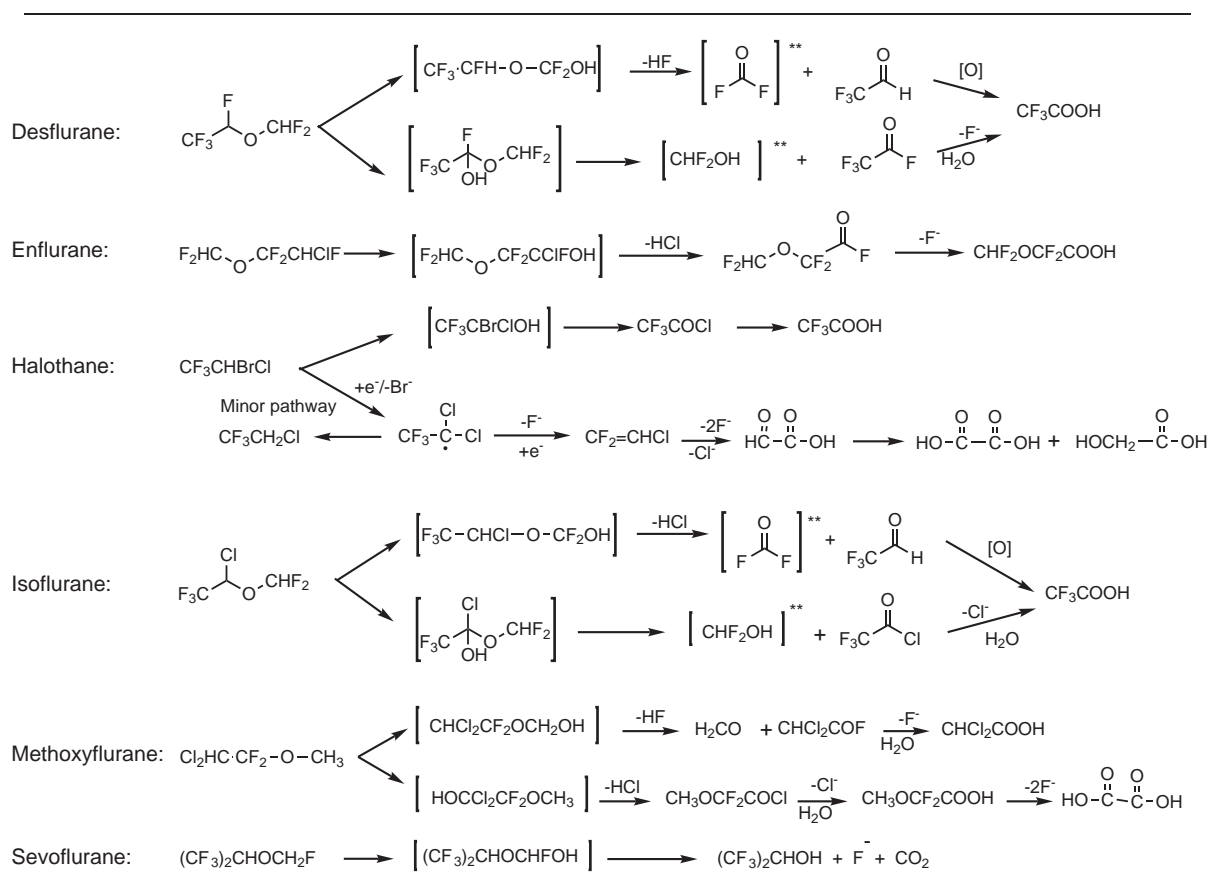
^aIndicates stability to soda lime, ultraviolet light, and common metals.

the carbon-halogen bonds contributes to its nonflammability, volatility, and high lipid solubility (blood/gas partition coefficient = 2.3). This clear liquid with a sweet odor was developed based on predictions that its halogenated structure would provide chemical stability, an intermediate blood solubility, and significant anesthetic potency. Halothane is the only useful volatile anesthetic possessing a bromine atom, which has been suggested to contribute to its potency. Similarly, the addition of fluorine atoms, of which halothane has three, contributes to its increased potency, volatility, and relative chemical stability of the hydrocarbon skeleton (Table 16.5).

Halothane produces rapid onset and recovery from anesthesia with high potency when used alone or in combination with nitrous oxide. Most metals, with the exception of chromium, nickel, and titanium, are easily tarnished by halothane. Although halothane is relatively stable, it is subject to spontaneous oxidative decomposition to hydrochloric acid (HCl), hydrobromic acid (HBr), and phosgene (COCl_2). For this reason, it comes in dark, amber glass containers with thymol added as a preservative to minimize decomposition. Halothane can permeate into the rubber components of the anesthetic

delivery devices, which might account for some slowing of the induction onset and recovery. Approximately 20% of an administered dose is metabolized, which accounts, in part, for the increased hepatotoxicity observed with this agent (Fig. 16.7).

ENFLURANE Enflurane (Fig. 16.6) was introduced into medical practice in the United States in 1973 and is a clear, colorless, nonflammable liquid with a mild, sweet odor. Although relatively stable chemically, enflurane does not attack aluminum, copper, iron, or brass and is soluble in rubber, which can prolong induction/recovery times, as seen with halothane (Table 16.5). Enflurane has an intermediate solubility in blood (blood/gas partition coefficient = 1.9) and significant potency. Most of its pharmacologic properties are similar to those of halothane, although there can be slightly less nausea, vomiting, arrhythmias, and postoperative shivering than observed with halothane. High concentrations of enflurane, however, are more likely to produce convulsions and circulatory depression. Enflurane also relaxes the uterus and, thus, should not be used as an anesthetic during labor. Metabolism via CYP2E1 accounts for 2% of an



Data from references 28 and 29.

Decomposition of unstable intermediates: $\text{CF}_2\text{O} \rightarrow 2\text{F}^- + \text{CO}_2$; $\text{CHF}_2\text{OH} \rightarrow 2\text{F}^- + \text{HCOOH}$;

FIGURE 16.7 Proposed metabolites of fluorinated anesthetics.

inhaled dose and includes metabolism to form a fluoride ion and fluoromethoxydifluoroacetic acid (Fig. 16.7) (30). During recovery, enflurane leaves the fatty tissues rapidly and, therefore, is not available for a prolonged period of time for significant metabolism to proceed.

ISOFLURANE Isoflurane (Fig. 16.6) was introduced in the United States in 1981 and is a potent anesthetic agent with many similarities to its isomer enflurane (potent, nonflammable, and intermediate blood solubility; with blood/gas partition coefficient = 1.4). However, it does produce significantly fewer cardiovascular effects than enflurane and can be used safely with epinephrine without a concern for arrhythmia production. Isoflurane has a more pungent odor than halothane and, thus, can cause irritation to the throat and respiratory tract, triggering coughing and laryngospasm. To overcome this problem, it is often supplemented with intravenous agents. Less than 0.2% of an administered dose is metabolized, mostly to fluoride and trifluoroacetic acid (Fig. 16.7). As discussed below, some minimal potential for hepatotoxicity is associated with a trifluoroacetyl halide metabolite.

A comparative assessment of the volatile anesthetic properties of enflurane, halothane, and isoflurane is shown in Table 16.6.

DESFLURANE Desflurane (Fig. 16.6) was introduced in the United States in 1992 and is a pungent, volatile agent that is nonflammable and noncorrosive to metals. With poor blood solubility (blood/gas partition coefficient = 0.42), similar to that of nitrous oxide, desflurane rapidly induces anesthesia. Because the boiling point

of desflurane is close to room temperature, a specially designed, heated vaporizer is used to deliver the anesthetic with appropriate concentrations of oxygen either alone or in combination with nitrous oxide. Recovery from the anesthetic state is also rapid, being approximately twice as rapid as that with isoflurane. Because of the rapid induction and recovery associated with desflurane, this anesthetic has gained popularity in outpatient surgical procedures. Desflurane is rather pungent, so patients often are induced with an intravenous anesthetic agent and then maintained with desflurane. Desflurane is not metabolized to any great extent and, therefore, has not been associated with hepatotoxicity or nephrotoxicity (31). Metabolites, mostly trifluoroacetate, account for less than 0.02% of the administered dose (Fig. 16.7). Although desflurane can react with soda lime or Baralyme to form carbon monoxide, no reports of adverse outcomes in patients have appeared.

SEVOFLURANE Sevoflurane (Fig. 16.6) is a nonflammable, nonirritating, pleasant-odored volatile anesthetic available for use in the United States. Similar to desflurane in many of its pharmacologic actions, except sevoflurane which has low blood solubility (blood/gas partition coefficient = 0.60), higher potency, and the advantage of not being irritating to the respiratory tract. Induction and recovery are rapid. Sevoflurane undergoes significantly more metabolism (CYP2E1) than desflurane, however, and as much as 3% of an administered dose can be recovered as hexafluoroisopropanol (Fig. 16.7). Some fluoride ion can also be produced, but the incidence of nephrotoxicity or hepatotoxicity appears low, especially when used infrequently for short periods of time. There have been concerns regarding the reactivity of sevoflurane with soda lime or Baralyme, in which a potentially toxic olefin byproduct termed “Compound A” (2-(fluoromethoxy)-1,1,3,3,3-pentafluoro-1-propene) can be formed. With appropriate precautions, however, sevoflurane can be used safely in both children and adults.

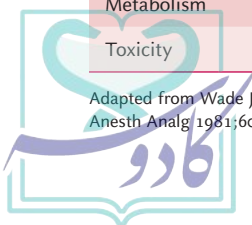
METHOXYFLURANE Methoxyflurane (Fig. 16.6) is seldom used because of its propensity to cause renal toxicity. It is the most potent of the agents discussed here, and it has high solubility in blood (blood/gas partition coefficient = 12). Induction and recovery would be expected to be slow. Chemically, it is rather unstable, and as much as 50% of an administered dose can be metabolized. Toxic metabolites significantly limit its utility as a general anesthetic (Fig. 16.7).

TOXICITY OF FLUORINATED GENERAL ANESTHETICS Although few signs of toxicity usually are observed during the short-term, infrequent administration of general anesthetics, a few well-defined toxic effects have been noted. For instance, halothane and methoxyflurane are known to produce hepatotoxicity and nephrotoxicity, respectively. Both of these toxic reactions are believed to result from highly reactive metabolites of the parent compound.

TABLE 16.6 Comparative Assessment of Enflurane (E), Halothane (H), and Isoflurane (I)

Property	Superior	Intermediate	Inferior
Stability	I = E	—	H
Blood solubility	I	E	H
Pungency	H	I	E
Respiratory depression	H	I	E
Circulatory depression	I	H	E
Induction of arrhythmias	I	E	H
Muscle relaxation	I = E	—	H
Increased intracranial pressure/cerebral blood flow	I	E	H
Seizure activity	H = E	—	E
Metabolism	I	E	H
Toxicity	I	E	H

Adapted from Wade JC, Stevens WC. Isoflurane: an anesthetic for the eighties? *Anesth Analg* 1981;60:666–682; with permission.



Overall, however, the therapeutic ratio for most of the general anesthetics approaches 4:1 (32).

Hepatotoxicity Hepatitis caused by halothane occurs in 1 in 20,000 patients exposed to this anesthetic and is thought to result from the binding of a reactive free radical metabolite to liver tissue (Fig. 16.7). The resultant abnormal molecular product in the liver is viewed by the immune system as a foreign substance (i.e., an antigen), which then sensitizes cells to produce antibodies. Some have suggested that the trifluoroacetyl halide metabolite is responsible for the initiation of halothane hepatitis. Interestingly, both enflurane and isoflurane can be metabolized to the acylated halides and produce a similar immune-mediated syndrome, although to a much lesser extent. Additionally, there appears to be cross-reactivity among these three agents, because the antigen formed is similar enough in structure to elicit the immune system response. Some investigations have suggested that a genetic susceptibility factor could be responsible, in part, for this serious form of hepatitis.

Halothane also can produce another form of hepatotoxicity. This is a self-limiting hepatic dysfunction characterized by elevated liver transaminase enzymes, which probably results from impaired oxygenation of the hepatocytes during exposure to this anesthetic. Isoflurane and enflurane have also been reported to produce a similar elevation of liver enzymes, although to a lesser extent than halothane.

Malignant Hyperthermia This rare (1 in 15,000 anesthetic uses) but potentially fatal complication associated with the use of certain anesthetics (e.g., halothane) is characterized by a rapid rise in core body temperature associated with hypermetabolic reactions in the skeletal muscle of genetically susceptible subjects. Such individuals appear to have an autosomal dominant-mediated defect in the Ca^{2+} -release channel commonly referred to as the ryanodine receptor. The large amounts of heat generated, massive increase in oxygen consumption, and production of carbon dioxide can quickly lead to death or permanent neurologic damage unless appropriate supportive treatment, including rapid cooling, 100% oxygen, and control of acidosis, is promptly initiated. The administration of the skeletal muscle relaxant dantrolene, which blocks release of Ca^{2+} from the sarcoplasmic reticulum, reduces muscle rigidity and heat production, which significantly improves the prognosis of the patient. Besides the fluorinated volatile anesthetics, some depolarizing neuromuscular blocking agents (e.g., succinylcholine) and some neuroleptics (e.g., haloperidol) are also reportedly associated with similar malignant hyperthermic syndromes, although the underlying mechanism mediating these can differ somewhat from those associated with the general anesthetics.

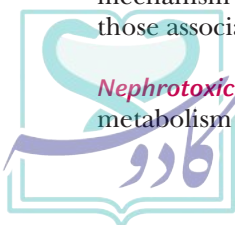
Nephrotoxicity Fluorinated anesthetics that undergo metabolism to form inorganic fluoride ion have the

potential to produce damage to the renal tubular cells. Of the fluorinated anesthetics, methoxyflurane is the only agent commonly associated with nephrotoxicity. Methoxyflurane is metabolized (Fig. 16.7) to produce plasma fluoride ion levels in excess of the threshold value for renal damage of 40 $\mu\text{mol/L}$. Others, such as sevoflurane, have only very rarely been associated with nephrotoxicity—and then usually in patients with severe renal compromise. Plasma levels of fluoride only reach 15 to 20 $\mu\text{mol/L}$ following 2.5 MAC-hour exposure to enflurane (33). The rates of metabolic defluorination of the useful anesthetic agents are as follows: methoxyflurane > enflurane = sevoflurane > isoflurane > desflurane = halothane.

Low-level Chronic Exposure Typically, patients are exposed to greater-than-MAC concentrations of the volatile anesthetics for limited periods of time, such as a number of hours during a surgical procedure, and not for extended periods of time (e.g., days or weeks). Because surgical and dental personnel, however, can be exposed to low levels of the general anesthetics for prolonged periods over many years or even decades, the ability of such agents to produce chronic toxicity is of paramount concern. Although the occupational exposure to these agents has been minimized with improved waste gas-scavenging devices, some epidemiologic studies have demonstrated increased levels of spontaneous abortions, congenital birth defects in offspring, and increased rates of certain cancers in chronically exposed medical personnel (34).

Nitrous Oxide

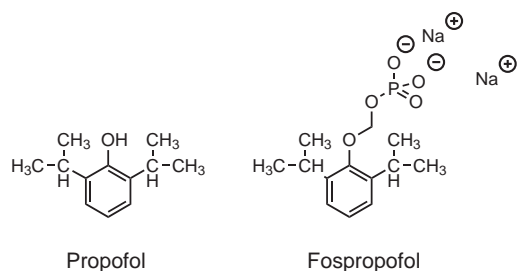
Commonly called “laughing gas,” nitrous oxide (N_2O) is a gas at room temperature, the least potent of the inhalation anesthetics used today and poor blood solubility (blood/gas partition coefficient = 0.47) (Table 16.5). With an MAC value in excess of 105%, this colorless, tasteless, and odorless to slightly sweet-smelling gas is not normally capable of producing surgical anesthesia when administered alone. The MAC for nitrous oxide has been demonstrated to be between 105% and 140% and, thus, cannot achieve surgical anesthesia under conditions at standard barometric pressure. To demonstrate that the MAC was greater than 100%, Bert in 1879 used a mixture of 85% nitrous oxide with oxygen at 1.2 atmospheres in a pressurized chamber. Only at this elevated pressure could an MAC adequate for surgical anesthesia be achieved. Decreasing the oxygen content of a nitrous oxide mixture to values less than 20% to allow an increase in the concentration of nitrous oxide to greater than 80% can be dangerous, because hypoxia would be expected to result. Thus, when administered alone, nitrous oxide finds utility as an anesthetic agent during certain procedures (e.g., dental) in which full surgical anesthesia is not required. Most commonly, however, nitrous oxide is used in combination with other general anesthetics, because it is capable of decreasing the concentration of the added anesthetic required to produce an adequate depth of anesthesia for surgical procedures.



Although no firm underlying mechanisms have been demonstrated, some authors have suggested that irreversible oxidation of the cobalt atom in vitamin B₁₂ by nitrous oxide can lead to inactivation of enzymes dependent on this vitamin, with resultant metabolic aberrations. Such examples have included methionine synthetase and thymidylate synthetase, which are essential in the synthetic pathways leading to the production of myelin and thymidine, respectively. Should these enzymes be impaired during the sensitive periods of in utero development, the potential for malformations can unfortunately be realized. To date, no studies have been able to demonstrate conclusively that low-level exposure to nitrous oxide is associated with a meaningful disruption of crucial metabolic functions to produce the above-described toxicity; however, measures including improved waste gas-scavenging systems should be taken to minimize exposure of personnel.

Clinically Useful Intravenous General Anesthetic Agents

Propofol



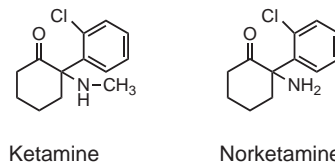
One of the most commonly used parenteral anesthetics used in the United States is propofol (Diprivan). Used intravenously, propofol is not chemically related to the barbiturates or other intravenous anesthetics. Propofol appears to act via enhancing GABAergic neurotransmission within the CNS. This occurs most likely at the GABA_A receptor complex, but at a site distinct from where the benzodiazepines bind. Because of its poor water solubility (partition coefficient ~6,200), propofol is formulated as a 1% or 2% emulsion with soybean oil, egg lecithin, and glycerol. Sodium metabisulfite (an antioxidant) or ethylenediaminetetraacetic acid (metal chelating agent) is also included in the parenteral dosage form for stability. Because of the likelihood of bacterial contamination of open containers, propofol should be either administered or discarded shortly after sterility seals are broken. Following intravenous administration of a dose of 2.0 to 2.5 mg/kg, a state of hypnosis is achieved within 30 to 60 seconds, which lasts for approximately 5 to 10 minutes. A longer anesthetic state can be achieved by additional propofol dosing or, as typically is the case, maintenance with a volatile anesthetic agent. Blood pressure and heart rate usually are decreased following propofol administration. Propofol is highly bound to plasma proteins (approximately 98%). Metabolism of propofol proceeds

rapidly via hepatic conversion to its glucuronide and sulfate conjugates, with less than 0.3% excreted unchanged. Because this agent produces a rapid induction and recovery and is infrequently associated with episodes of vomiting, propofol has found utility as an anesthetic agent in outpatient surgical environments.

Fospropofol

Due to its water solubility, the phosphate ester prodrug of propofol (Lusedra), fospropofol, avoids the emulsion formulation concerns described earlier for propofol. All of the pharmacodynamic effects of fospropofol are attributed to propofol, which is liberated following hydrolytic metabolism by serum alkaline phosphatases. Typical dosing is 6.5 mg/kg, with supplemental doses of 1.6 mg/kg as needed. While formaldehyde and phosphate are also released by this metabolic conversion, the levels of these compounds do not increase to levels beyond those normally found endogenously and thus do not pose any toxicity concerns, except perhaps in overdose situations. Due to its requirement for conversion to the active propofol, the onset of fospropofol is delayed (4 to 10 minutes) when compared to that for propofol (30 to 60 seconds) and has a prolonged duration of anesthetic action.

Ketamine

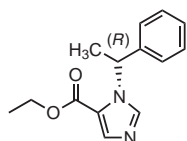


Ketamine hydrochloride is an injectable, very potent, rapidly acting anesthetic agent. As with propofol, its duration of anesthetic activity is also relatively short (10 to 25 minutes). Ketamine does not relax skeletal muscles and, therefore, can only be used alone in procedures of short duration that do not require muscle relaxation. Recovery from anesthesia can be accompanied by "emergence delirium," which is characterized by visual, auditory, and confusional illusions. Disturbing dreams and hallucinations can occur up to 24 hours after the administration of ketamine. Its elimination half-life is 2 to 3 hours, and its volume of distribution is 2 to 3 L/kg. Ketamine has an oral bioavailability of less than 16%. Termination of the acute action of ketamine is largely a result of its redistribution from the brain into other tissue; however, the formation of the glucuronide conjugate and metabolism in the liver to a number of metabolites does occur. One of these metabolites of interest, norketamine, is formed via the action of CYP2B6. This *N*-demethylated derivative retains significant activity at the NMDA receptor and can account for some of the longer-lasting effects of this anesthetic agent. Eventual conversion of norketamine to hydroxylated metabolites and subsequent conjugation leads to metabolites that can be renally eliminated. Less than 4% of a dose is excreted unchanged in the urine.

Ketamine is capable of producing a “dissociative” anesthesia, which is characterized by EEG changes indicating a dissociation between the thalamocortical and limbic systems (35). These neuronal systems, which normally are associated with one another, help to maintain the neuronal connections required for consciousness. When dissociated, the subject will appear to be cataleptic, with the eyes open in a slow, nystagmic gaze (oscillating movement of the eyeball) (1). A potent analgesic and amnesic effect is produced, as is an increase in muscle tone in some areas. Although patients can appear to be awake, they are incapable of communicating and do not remember the event or the people around them. Blood pressure and heart rate usually are increased following ketamine administration.

Ketamine appears to act similarly to phencyclidine (PCP; also known as Angel Dust), which acts as an antagonist within the cationic channel of the NMDA receptor complex (36). By preventing the flow of cations through this channel, ketamine prevents neuronal activation, which normally is required for the conscious state. The analgesic activity of ketamine, however, is more likely the result of an interaction with an opioid receptor or the less well-understood non-opioid sigma receptor. Other studies have suggested a possible involvement of serotonin receptors and muscarinic receptors (37). Ketamine, like PCP, has a significant potential for abuse.

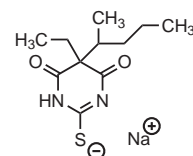
Etomidate



R-Etomidate

Etomidate is the ester of a carboxylated imidazole, with a partition coefficient of 2,000 and a weak base pK_a of 4.5, that is available as the *R*(+)-isomer solubilized in 35% propylene glycol for intravenous injection in addition to being available for rectal administration. It is a potent, short-acting hypnotic agent (<3 minutes) without analgesic activity and with a rapid onset of action. This agent is useful for the induction of anesthesia in hemodynamically unstable patients prone to hypotension because of hypovolemia, coronary artery disease, or cardiomyopathies. Recovery is similarly rapid following discontinuance of the drug. Etomidate is hydrolyzed by hepatic esterases to the corresponding inactive carboxylic acid, with subsequent renal and biliary excretion terminating its action. Its apparent elimination half-life is approximately 5 to 6 hours, with a volume of distribution of 5 to 7 L/kg. Changes in hepatic blood flow or hepatic metabolism will have only moderate effects on etomidate disposition. Concerns regarding the ability of etomidate to precipitate myoclonic jerks and inhibit adrenal steroid synthesis have been reported.

Ultrashort-Acting Barbiturates



Thiopental

Thiopental, an ultrashort-acting barbiturate (partition coefficient ~390), is used intravenously to produce a rapid unconsciousness for surgical and basal anesthesia. This agent is used initially to induce anesthesia, which then can be maintained during the surgical procedure with a general anesthetic agent. The induction typically is very rapid and pleasant. (The ultrashort-acting barbiturates are discussed in Chapter 15.)

LOCAL ANESTHETICS

Local anesthetic agents are drugs that, when given either topically or administered directly into a localized area, produce a state of local anesthesia by reversibly blocking nerve conductances that transmit the sensations of pain from this localized area to the brain. Unlike the anesthesia produced by general anesthetics, the anesthesia produced by local anesthetics is without loss of consciousness or impairment of vital central cardiorespiratory functions. Local anesthetics block nerve conductance by binding to selective sites on the Na^+ channels in the excitable membranes, thereby reducing Na^+ passage (i.e., conductance) through the pores and, thus, interfere with the generation of action potentials. Although local anesthetics decrease the excitability of nerve membranes, they do not affect the neuron's resting potential. Local anesthetics, in contrast to analgesic compounds, do not interact with the pain receptors or inhibit the release or the biosynthesis of pain mediators.

The Discovery of Local Anesthetics

As with many modern drugs, the initial leads for the design of clinically useful local anesthetics originated from natural sources. As early as 1532, the anesthetic properties of coca leaves (*Erythroxylon coca* Lam) became known to Europeans from the natives of Peru, who chewed the leaves for a general feeling of well-being and to reduce hunger. Saliva from chewing the leaves was often used by the natives to relieve painful wounds. The active principle of the coca leaf, however, was not discovered until 1860 by Niemann, who obtained a crystalline alkaloid from the leaves, to which he gave the name cocaine, and who noted the anesthetic effect on the tongue (see Fig. 16.8 for structure of cocaine). Although Moréno y Maiz in 1868 first asked the question of whether cocaine could be used as a local anesthetic, Von Anrep in 1880, after many animal experiments, recommended that cocaine

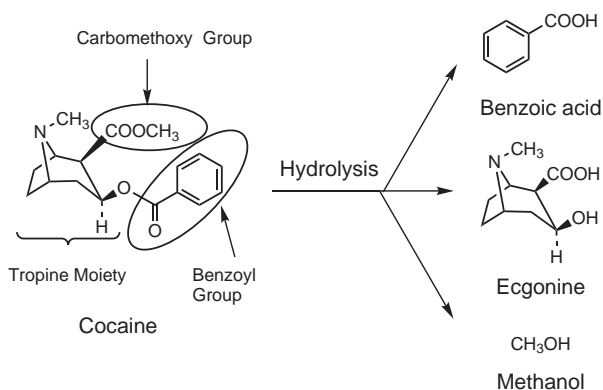
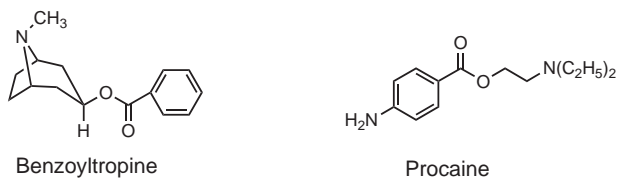


FIGURE 16.8 Structures of cocaine and its hydrolysis products.

be used clinically as a local anesthetic. The first report of successful surgical use of cocaine appeared in 1884 by Koller, an Austrian ophthalmologist. This discovery led to the rapid development of new local anesthetic agents and anesthetic techniques (38).

Cocaine dependence (or addiction) is psychological dependency on the regular use of cocaine. The use of cocaine, depending on the severity, can cause mood swings, paranoia, insomnia, psychosis, high blood pressure, tachycardia, panic attacks, cognitive impairments, and drastic changes in the personality that can lead to aggressive, compulsive, criminal, and/or erratic behaviors. The symptoms of cocaine withdrawal range from moderate to severe: dysphoria, depression, anxiety, psychological and physical weakness, pain, and compulsive craving.

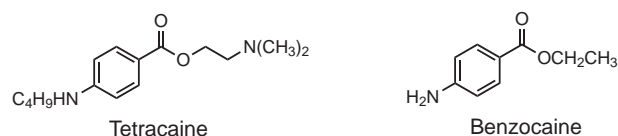
Although the structure of cocaine was not known until 1924, many attempts were made to prepare new analogs of cocaine that lacked its addicting liability and other therapeutic shortcomings, such as allergic reactions, tissue irritations, and poor stability in aqueous solution. Also, cocaine is easily decomposed to hydrolysis products, ecgonine and benzoic acid, when the solution is sterilized (Fig. 16.8).



When the chemical structure of ecgonine became known, the preparation of active compounds containing the ecgonine nucleus accelerated. It was soon realized that a variety of benzoyl esters of amino alcohols, including benzoyltropine, exhibited strong local anesthetic properties without any of cocaine's addiction liability. Thus, removal of the 2-carbomethoxy group from cocaine also abolished its addiction liability. This discovery eventually led to the synthesis of procaine in 1905 (known as Novocain), which then became the prototype for local anesthetics for nearly half a century, largely because it lacked the severe local and systemic toxicities of cocaine.

Although the intrinsic potency of procaine was low and its duration of action relatively short compared with that of cocaine, it was found that these deficiencies could be remedied when procaine was combined with a vasoconstrictor, such as epinephrine. Vasoconstrictor agents reduce the local blood supply and, thereby, prolong the residence time of the local anesthetic at the injection site.

Following the introduction of procaine, hundreds of structurally related analogs were prepared and their local anesthetic properties examined in an attempt to identify agents with enhanced potency and duration of action compared to the weak and short-acting procaine. Among these compounds, tetracaine remains the most potent, long-acting, ester-type local anesthetic agent, which is used in spinal anesthesia.



The topical anesthetic agent benzocaine was synthesized by Ritsert in 1890 and found to have good anesthetizing properties and low toxicity. However, due to its limited water solubility, except at low pH values as a result of the lack of a basic aliphatic amino group, the preparation of pharmaceutically acceptable parenteral solutions could not be achieved.



The serendipitous discovery of the local anesthetic activity of another natural alkaloidal product, isogramine, in 1935 by von Euler and Erdtman was the next major turning point in the development of clinically useful local anesthetic agents. This observation led to the synthesis of lidocaine (Xylocaine) by Löfgren in 1946; lidocaine was the first nonirritating, amide-type local anesthetic agent with good local anesthetic properties yet less prone to allergic reactions than procaine analogs, and was found to be stable in aqueous solution due to its more stable amide functionality. Structurally, lidocaine can be viewed as an open-chain analog of isogramine and, thus, is a bioisosteric analog of isogramine.

Since the discovery of lidocaine in the 1940s, much more progress has been achieved in the fields of neurophysiology and neuropharmacology than in the synthesis of local anesthetics by medicinal chemists. Most of this research has significantly increased our understanding of how nerve conduction occurs and how compounds interact with the neuronal membranes to produce local anesthesia. It should be noted, however, that although a number of current clinically useful local anesthetic

agents have been introduced into the market, the ideal local anesthetic drug has, unfortunately, not yet been realized.

Characteristics of an Ideal Local Anesthetic

The ideal local anesthetic should produce reversible blockade of sensory neurons with a minimal effect on the motor neurons. It also should possess a rapid onset, have a sufficient duration of action for the completion of major surgical procedures without any systemic toxicity, and be easily sterilized and not inordinately expensive (Table 16.7). Hopefully through further structure–activity relationship studies, particularly with regard to their selective actions on the voltage-gated Na^+ channels, the ideal local anesthetic agent can be realized. Additional leads for the design of ideal local anesthetics could also come from a more systematic metabolic and toxicity study of currently available agents. To understand the chemical aspects of local anesthetics and, thus, to provide a proper background for practical uses of these compounds, it is necessary to have a working knowledge of basic neuroanatomy and electrophysiology of the nervous system.

Neuroanatomy and Electrophysiology of the Nervous System

Neuroanatomy

Sensory neurons (afferent neurons) transmit sensory electrochemical impulses from sensory endings (receptors) in the skin and other sensory organs toward the CNS (i.e., brain and spinal cord) where the information is processed. On the other hand, motor neurons (efferent neurons) transmit electrochemical impulses from the CNS toward motor endings or other target (effector) cells that, when stimulated, produce a response such as contraction of muscle or stimulation/inhibition of sweat glands or exocrine glands. The transmission of a nerve impulse along an axon occurs

TABLE 16.7 Characteristics of the Ideal Local Anesthetic Agent

Produces a reversible blockade
Selective for sensory neurons with no effect on motor neurons
Rapid onset
Sufficient duration of action
Chemically stable when sterilized
No systemic toxicity
Wide margin of safety
Compatible with other coadministered drugs
Absence of adverse effects
Inexpensive

as a result of electrochemical changes in the Na^+ and K^+ potential across the neuronal membrane. Such neurons are bundled together into a cable-like structure and wrapped in a connective tissue sheath (the perineurium), called a nerve. Within a nerve, each axon is wrapped by a layer of connective tissue called the endoneurium. Finally, the entire nerve is wrapped in a layer of connective tissue called the epineurium (much like an electrical cable of wires wrapped with a plastic casing), as shown in Figure 16.9. (39). A nerve provides a common pathway for the transmission of electrochemical impulses. Thus, each nerve is a cord-like structure that contains groups of neurons in small bundles. The cell bodies of the sensory neurons are found at the point at which the nerve enters the vertebrae and can be seen as enlargements on the nerve bundles (spinal or dorsal root ganglion). The cell bodies (anterior horn cell) of the motor neurons are found within the gray matter of the spinal cord.

Figures 16.9 and 16.10 also illustrate that each axon has its own membranous covering, the endoneurium (often called the nerve membrane), which is tightly surrounded by a myelin sheath of the Schwann cell. The myelin sheath is not continuous along the fiber, with intermittent gaps or interruptions at the nodes of Ranvier, which serve to facilitate neuronal conduction.

Electrophysiology of Nerve Membrane

RESTING POTENTIAL Most nerves have a resting membrane potential (unstimulated or polarized state) of approximately -70 to -90 mV as a result of a slight imbalance of electrolyte ions (e.g., sodium, potassium, calcium, magnesium, and chloride) across the nerve membranes, between the intracellular cytoplasm and the extracellular fluid (40). In the polarized state, the nerve membrane is somewhat impermeable to Na^+ as seen by the low intracellular Na^+ concentration, whereas K^+ flows in and out of the cell with greater ease, indicating that the neuronal membrane is highly permeable to K^+ . A high K^+ concentration is retained intracellularly by the attractive forces

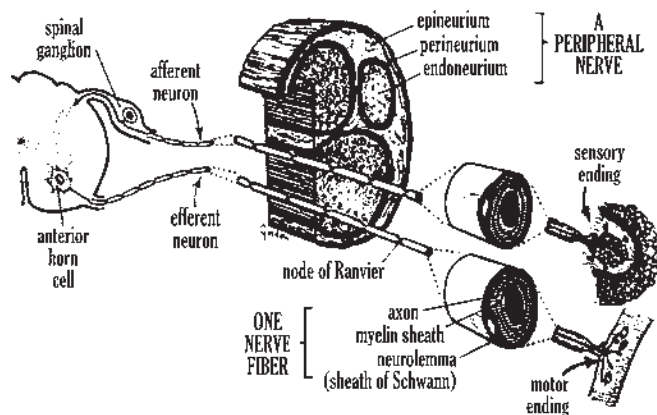


FIGURE 16.9 Diagram showing the various parts of a peripheral nerve. (Adapted from Ham AW. Histology, 6th Ed. Philadelphia: JB Lippincott, 1969:524, with permission.)

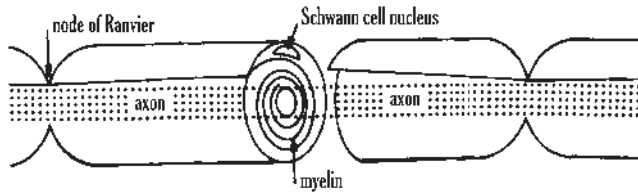


FIGURE 16.10 Single myelinated nerve fiber.

provided by the negatively charged intracellular protein molecules. Thus, the predominant intracellular cations are K^+ (~110 to 170 mmol/L), and the predominant extracellular cations are Na^+ (~140 mmol/L) and chloride (~110 mmol/L).

Because changes in the intracellular or extracellular concentration of K^+ would be expected to markedly alter the resting membrane potential, electrophysiologists modeled the excitable cell as if it were an electrochemical, or Nernst, cell. Thus, the resting potential for K^+ can be determined by the familiar Nernst equation:

$$E = -RT/zF \ln [K^+]_i / [K^+]_o$$

in which E = membrane potential, intracellular minus extracellular; R = gas constant; T = temperature; z = ion valence; F = Faraday's constant; $[K^+]_i$ = activity of intracellular K^+ ; and $[K^+]_o$ = activity of extracellular K^+ .

ACTION POTENTIAL In most cells, action potentials are transient transmembrane depolarizations that result from the influx of Na^+ through a brief opening of the voltage-gated Na^+ channels upon excitation of the cell (40). The transmembrane potential during an action potential changes from -70 to approximately $+40$ mV (a total net change of 110 mV) (depolarized state) and then promptly returns to the resting (polarized state) potential; the entire event typically lasts approximately 1 millisecond (Fig. 16.11). An action potential is capable of traveling long distances along the neuron because open Na^+ gates stimulate neighboring Na^+ gates to open.

The transmembrane potential for Na^+ at the peak of its action potential can be predicted from the Nernst equation by substituting appropriate Na^+ concentrations for those of K^+ . Thus, it appears that the excitable nerve membrane can be transformed from a potassium electrode to a sodium electrode during the active process (41).

As the cell approaches its peak action potential, the membrane permeability to Na^+ again decreases (Na^+ inactivation). If no other event occurred, this cell would slowly return to its resting potential, but the cell again becomes highly permeable to K^+ , allowing K^+ to flow out into extracellular fluid and quickly restore the membrane potential (repolarization). After an action potential, the cell would therefore be left with a small increase in Na^+ and a decrease in K^+ . To explain how the nerve is restored to its original electrolyte composition at the resting potential, it is necessary to postulate a mechanism

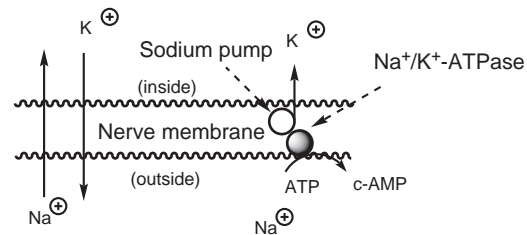
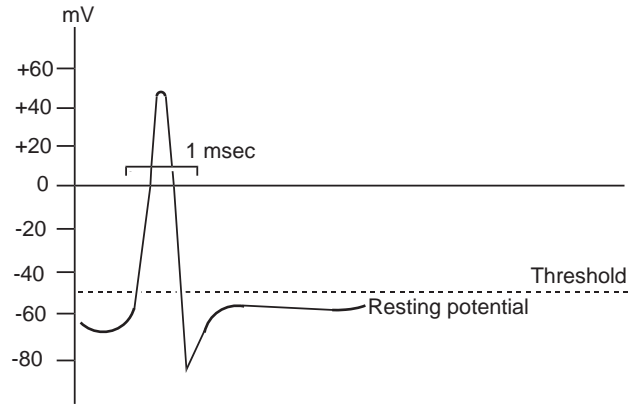


FIGURE 16.11 Relationship between membrane action potential and ionic flux across the nerve membrane.

by which intracellular Na^+ could be rapidly transported (effluxed) from inside the membrane to the outside extracellular fluid and extracellular K^+ could be transported (influxed) from extracellular fluid to inside the membrane. This is accomplished by the “sodium pump,” which requires energy from the splitting of adenosine triphosphate by sodium-potassium adenosine triphosphatase (Na^+/K^+ -ATPase) to adenosine monophosphate. This pump transports three Na^+ to the outside of the membrane for every two K^+ that enter the inside of the membrane.

THRESHOLD The voltage necessary to change localized electrochemical differences into a propagated action potential is called the threshold voltage, which is closely related to the stimulus duration—the longer the stimulus, the lower the threshold voltage. An electrical stimulus of less than a certain voltage can only result in local electrochemical changes and cannot elicit a propagated action potential.

REFRACTORINESS A state of absolute refractoriness (i.e., complete inexcitability) occurs immediately after an impulse has been propagated, and no stimulus, no matter how strong or long, can produce an excited state. Shortly thereafter, the axon becomes relatively refractory; it responds with a propagated impulse only to stimulation that is greater than the normal threshold. The length of the refractory period is affected by the frequency of stimulation and by many drugs (Fig. 16.12).

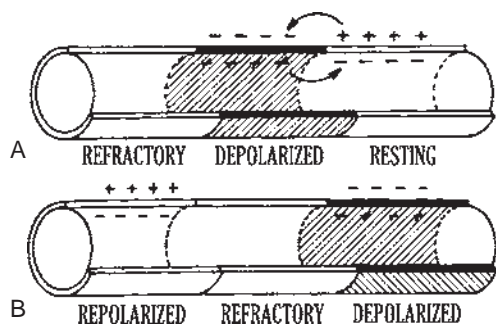


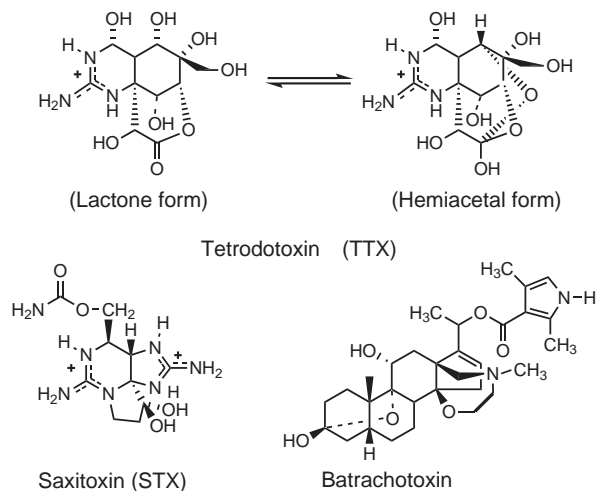
FIGURE 16.12 Impulse propagation. (A) The wave of depolarization passes down the nerve, followed by a wave of refractoriness. (B) The wave of refractoriness is followed by a wave of repolarization. (Adapted from De Jong RH, Freund FG. *Physiology of peripheral nerve and local anesthesia*. *Int Anesthesiol Clin* 1970;8:35–53, with permission.)

CONDUCTANCE VELOCITY AND NODAL CONDUCTION The conduction velocity is the velocity at which an impulse is conducted along the nerve and is proportional to the diameter of the axon. Because longitudinal resistance is inversely proportional to cross-sectional area, impulses are conducted faster in large-diameter axons. The squid giant axon, used in many neurophysiology investigations, is unmyelinated and exceptionally large (~500 to 1,000 μm); therefore, impulses are conducted rapidly along the axon. However, contraction of the mantle of a squid, which this axon controls, is an uncomplicated procedure that does not require a complex sensorimotor feedback system. Perhaps during evolution, vertebrates developed a complicated input–output system of many axons collected in bundles, as shown in Figure 16.9.

Conduction along these neurons would be slow if they were not insulated with a myelin coat of connective tissue, interrupted at intervals by the nodes of Ranvier, where electrical current enters and exits. These ionic fluxes occurring at the nodes allow the electrical impulse to jump along the axon from node to node much faster than could occur in an unmyelinated axon (42).

SODIUM CHANNEL The voltage-gated Na^+ channels are discrete, membrane-bound glycoproteins that mediate Na^+ permeability and, thus, are responsible for the generation of action potentials in skeletal muscle, nerve, and cardiac tissues (43–50). Our understanding of the structural domains and binding sites on voltage-gated Na^+ channels has evolved considerably since the first cloning and expression studies of the channel protein by Noda (43). The channel gating kinetics have been extensively studied with the use of selective blockers of Na^+ channels, such as tetrodotoxin (TTX) and saxitoxin (STX), and by site-directed mutagenesis (49). Both TTX and STX bind stoichiometrically to the outer opening of the channels and are detected with patch-clamp electrophysiologic techniques on the cut-open squid giant axon (50). Neher and Sakmann, two German scientists, were awarded the

Nobel Prize in 1991 for physiology and medicine for their work on ion channels with these neurotoxins (50).



Recent mapping of receptor binding sites within the channel protein for lipid-soluble neurotoxins, such as batrachotoxin (BTX), and for local anesthetics using site-directed mutagenesis has provided further insight regarding these channels (49). For example, mammalian voltage-gated Na^+ channels contain one large α -subunit and one or two smaller β -subunits (15). The primary structure of the α -subunit is composed of four homologous domains (D1 to D4), each with six transmembrane segments (S1 to S6) and a hydrophobic loop thought to dip into the membrane to align the aqueous pore into a pseudotetrameric arrangement (Fig. 16.13) (47–49).

Furthermore, the voltage sensor for activation gating and the structure for fast inactivation gating have been delineated to involve the positively charged S4 segments of each domain (also known as the ion selectivity filter, which contains positively charged amino acid residues).

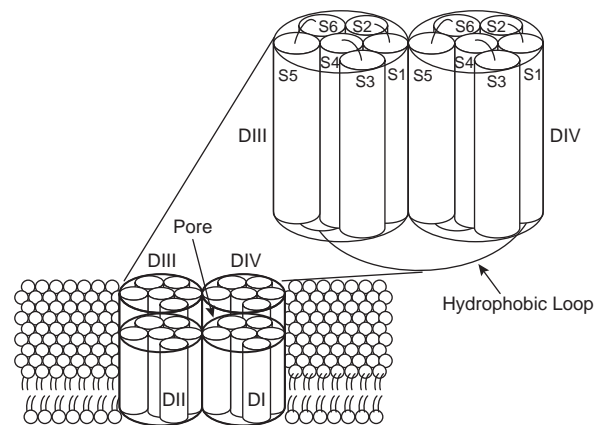


FIGURE 16.13 A schematic representation of the α subunit of the sodium channel and the pore-forming unit. (From Anger T, Madge DJ, Mulla M, et al. *Medicinal chemistry of neuronal voltage-gated sodium channel blockers*. *J Med Chem* 2001;44:115–137, with permission.)

The selective filter discriminates Na^+ from other ions (i.e., Na^+ passes through this pore approximately 12-fold faster than does K^+). Sodium channels open and close as they switch between several conformational states: the resting/closed form (polarized nonconducting state), the open channel (depolarized conducting state), and the inactivated form (polarized nonconducting state).

At resting potential, the Na^+ channels are in a resting/closed polarized state and are impermeable to the passage of Na^+ . On activation, the channels undergo conformational changes to an open depolarized state, allowing the rapid influx of Na^+ across the neuronal membrane.

Thus, when the threshold potential is exceeded, most of the Na^+ channels are in an open, or conducting, state. At the peak of the action potential, the open channels spontaneously convert to an inactivated polarized state by the “sodium pump” (i.e., nonconducting and non-activatable), leading to a decrease in Na^+ permeability. When a Na^+ channel is in the inactivated polarized state, it cannot be opened without first being transformed to the normal resting/closed form.

Therapeutic Considerations for Using Local Anesthetic Drugs

Since the discovery of cocaine in 1880 as a surgical local anesthetic, several thousand new compounds have been tested and found to produce anesthesia by blocking nerve conductance. Among these agents, approximately 20 are currently clinically available in the United States as local anesthetic preparations (Table 16.8). Table 16.9 contains chemical structures of the different types of agents in current or recent use.

Pharmaceutical Preparations

Local anesthetic agents generally are prepared in various dosage forms: aqueous solutions for parenteral injection, and creams and ointments for topical applications. Thus, chemical stability and aqueous solubility become primary factors in the preparations of suitable pharmaceutical dosage forms.

In general, compounds containing an amide linkage have greater chemical hydrolytic stability than do the ester types. In this regard, an aqueous solution of an amino ester-type local anesthetic is more likely to hydrolyze under normal conditions and cannot withstand heat sterilization as a result of base-catalyzed hydrolysis of the ester.

Local anesthetic activity usually increases with increasing lipid solubility. Unfortunately, this increase in lipid solubility is often inversely related to water solubility. For this reason, a suitable parenteral dosage form might not be available for these agents because of poor water solubility under acceptable conditions. For example, benzocaine, which lacks a sufficiently basic aliphatic amino group needed for salt formation, is insoluble in water at neutral pH. Protonation of the aromatic amino group in benzocaine results in a salt with a $\text{p}K_a$ of 2.78, which is too acidic and, therefore, unsuitable for use as a parenteral dosage form for injection. For this reason, benzocaine and its closely related analog, butamben, are used mostly in creams or ointments to provide topical anesthesia of accessible mucous membranes or skin for burns, cuts, or inflamed mucous surfaces.

Many attempts have been made to substitute oils, fats, or fluid polymers for the aqueous vehicle commonly used in injectable local anesthetics. Unfortunately, the pharmacologic results of these experiments have been quite disappointing, often as a result of the undesirable toxicity of the nonaqueous vehicle.

The only commonly accepted organic additives to local anesthetics are vasoconstrictors, such as epinephrine and levonordefrin (α -methylnorepinephrine). These compounds often increase the frequency of successful anesthesia and, to a limited degree, increase the duration of activity by reducing the rate of drug loss from the injection site, by constricting arterioles that supply blood to the area of the injection. The effect of these vasoconstrictors is less pronounced if the vasoconstrictors are added to a local anesthetic solution that is injected in an area that has profuse venous drainage but is remote from an arterial supply. By slowing the diffusion of the local anesthetic away from the targeted site of injection, the exposure of other tissues in the body is likely minimized such that the local anesthetic never reaches high enough concentrations to produce unwanted toxicities. However, there is a flip side to the benefit of the use of vasoconstrictors: A prolonged local anesthetic effect long after the surgical procedure is completed can lead to prolonged numbness and inadvertent soft tissue damage due to mechanical irritation (e.g., biting one's lip or tongue following dental procedures) as a result of the continued loss of pain sensations. Soft tissue injury to the lip in children 4 to 7 years of age following mandibular nerve block has been reported to be as high as 16%. Recently, an approach to reverse the vasoconstrictor-induced prolonged anesthetic state has utilized phentolamine, an α -adrenoceptor antagonist. Phentolamine mesylate in doses of 0.4 to 0.8 mg in adults and adolescents and 0.2

WHAT ARE THE SOURCES OF THESE NEUROTOXINS?

TTX is a potent neurotoxin isolated from the ovaries and liver of many marine species of Tetraodontidae, especially the Japanese fugu (or puffer fish). STX, produced by the marine dinoflagellates, *Gonyaulax catenella* or *Gonyaulax tamarensis*, is found concentrated in certain bivalve shellfish (e.g., mussels and clams). Consumption of contaminated mussels or clams causes paralytic shellfish poisoning, which is usually associated with toxic “red tide” environmental episodes in various coastal regions. BTX, a cardiotoxic and neurotoxic steroid isolated originally from the poisonous dart frog, *Phyllobates terribilis*, is a lipid-soluble neurotoxin that is at least 10-fold more toxic than TTX.

TABLE 16.8 Clinically Available Local Anesthetics

Generic Name	Trade Name	Recommended Application
Articaine	Septocaine, Septanest	Parenteral (dental)
Benoxinate	Oxybuprocaine	Mainly in ophthalmology
Benzocaine	Americaine, Anbesol, Benzodent, Orajel, Oratect, Rid-A-Pain, Hurracaine	Topical
Benzyl alcohol		Topical, mainly in combination with pramoxine
Bupivacaine	Marcaine, Sensorcaine	Parenteral
Butamben	Butesin	Topical
Chloroprocaine	Nesacaine	Parenteral
Dibucaine	Nupercainal, Cinchocaine	Topical
Dyclonine	Sucrets	Topical (mucosal only)
Etidocaine	Duranest	Parenteral
Ethyl chloride		Extracutaneous, temperature decreasing
Eugenol		Topical, especially in dentistry
Levobupivacaine	Chirocaine	Parenteral
Lidocaine	Xylocaine, L-Caine, DermaFlex, Dilocaine, Lidoject, Lignocaine, Octocaine,	Parenteral, topical
Mepivacaine	Carbocaine, Polocaine, Isocaine	Parenteral, topical
Menthol	Chloraseptic lozenges, Dermoplast, Pramegel, Pontacaine ointment	Topical, mainly in combination with benzocaine or pramoxine or tetracaine
Phenol	Anbesol	Topical, mainly in combination with benzocaine
Pramoxine	Prax, Tronothane	Topical
Prilocaine	Citanest	Parenteral, topical
Procaine	Novocain	Parenteral
Proparacaine	Alcaine, Ophthaine, Ak-Taine	Mainly in ophthalmology
Propoxycaine	Blockaine, Ravocaine	Parenteral
Ropivacaine	Naropin	Parenteral
Tetracaine	Pontocaine, Amethocaine, Prax	Parenteral, topical

to 0.4 mg in children reverses the vasoconstriction and allows for a more rapid diffusion of the local anesthetic from the injection site and a recovery of sensation (51).

Administration of a local anesthetic in a carbonic acid-carbon dioxide aqueous solution rather than the usual solution of a hydrochloride salt appreciably improves the time of onset and duration of action without causing increased local or systemic toxicity.

Carbon dioxide is believed to potentiate the action of local anesthetics by initial indirect depression of the axon, followed by diffusion trapping of the active form of the local anesthetic within the nerve. Use of the carbonate salt appears to be one pharmaceutical modification

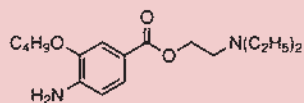
of the classic local anesthetic agents that can result in significant clinical advantages.

A Eutectic Mixture of a Local Anesthetic (EMLA) cream containing 2.5% lidocaine and 2.5% prilocaine (or etidocaine) is used for the topical application of local anesthetic through the keratinized layer of the intact skin to provide dermal or epidermal analgesia. This mode of administration allows the use of higher concentrations of local anesthetic with minimal local irritation and lower systemic toxicity. The use of EMLA creams, especially those containing prilocaine, on mucous membranes is not recommended, however, because of the faster absorption of the drugs and, therefore, the increasing

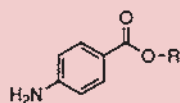
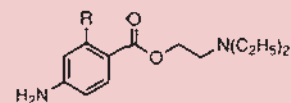
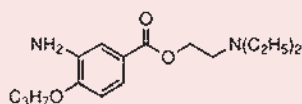


TABLE 16.9 Structures of Local Anesthetics

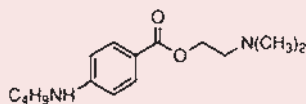
Amino Esters



Benoxinate (pKa = 9.0)

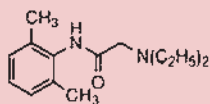
Benzocaine, R= C₂H₅ (pKa = 2.8)
Butamben, R= n-C₄H₉ (pKa = 2.5)Procaine, R= H (pKa = 8.8)
Chlorprocaine, R=Cl (pKa = 9.0)
Propoxycaïne, R=OC₃H₇ (pKa = 9.1)

Proparacaine (pKa = 9.1)

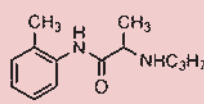


Tetracaine (pKa = 8.4)

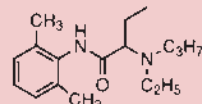
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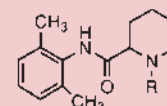
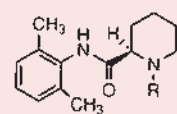
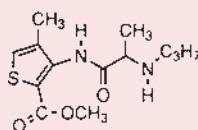
Lidocaine (pKa = 7.8)



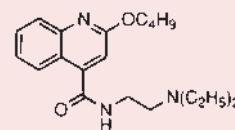
Prilocaine (pKa = 7.9)



Etidocaine (pKa = 7.7)

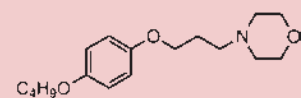
Mepivacaine, R= CH₃ (pKa = 7.6)
Bupivacaine, R= n-C₄H₉ (pKa = 8.1)Ropivacaine, R= n-C₃H₇ (pKa = 8.2)
Levobupivacaine, R= n-C₄H₉ (pKa = 8.1)

Articaine (pKa = 7.8)



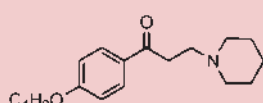
Dibucaine (pKa = 8.8)

Amino ethers



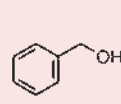
Pramoxine (pKa = 7.1)

Amino ketone

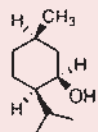


Dyclonine (pKa = 8.2)

Alcohols

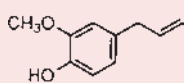


Benzyl alcohol



Menthol

Phenols



Eugenol



Phenol

risk of systemic toxicity, such as methemoglobinemia, specifically with prilocaine (52).

Toxicity and Side Effects

The side effects and toxicity of local anesthetics seem to be related to their actions on other excitable membrane proteins, such as in the Na⁺ and K⁺ channels in the heart, the nicotinic acetylcholine receptors in the neuromuscular junctions, and the nerve cells in the CNS. In general,

neuromuscular junctions and the CNS are more susceptible than the cardiovascular system to the toxic effects of local anesthetics.

The actions on skeletal muscles tend to be transient and reversible, whereas the CNS side effects can be more deleterious. The primary effect of the toxicity seems to be convulsions, followed by severe CNS depression, particularly of the respiratory and cardiovascular centers. This can be related to an initial depression of inhibitory

neurons, such as GABAergic systems, causing convulsions, followed by depression of other neurons, leading to general depression of the CNS.

The amino amide-type local anesthetics (i.e., lidocaine derivatives) are, in general, more likely to produce CNS side effects than the amino ester-type compounds (procaine analog). However, it should be noted that the toxic effects observed depend heavily on the route and site of administration as well as on the lipid solubility and metabolic stability of a given local anesthetic molecule. For example, most amide-type local anesthetics, such as lidocaine, are first degraded via *N*-dealkylation by hepatic enzymes (see Fig. 16.17). Unlike lidocaine, however, the initial metabolic degradation of prilocaine in humans is hydrolysis of the amide linkage to give *o*-toluidine and *N*-propylalanine. Formation of *o*-toluidine and its metabolites can cause methemoglobinemia in some patients (52). For this reason, prilocaine is much more likely than other local anesthetics to cause methemoglobinemia.

In contrast, allergic reactions to local anesthetics, although rare, are known to occur exclusively with *p*-aminobenzoic acid (PABA) ester-type local anesthetics (53). Whether the formation of PABA upon ester hydrolysis is solely responsible for this hypersensitivity remains to be determined. However, the preservative compounds, such as methylparaben, used in the preparation of amide-type local anesthetics are metabolized to the PABA-like substance, *p*-hydroxybenzoic acid. Thus, patients who are allergic to amino ester-type local anesthetics should be treated with a preservative-free amino amide-type local anesthetic.

Amide-type local anesthetics (e.g., procainamide and lidocaine) also possess antiarrhythmic activity when given parenterally and at a subanesthetic dosage. Although this action is likely an extension of their effects on Na⁺ channels in cardiac tissues, some evidence suggests a distinctly different mechanism of action with respect to the modulation of channel receptors and the location of binding sites for these compounds (54,55).

Chemical and Pharmacodynamic Aspects of Local Anesthetics

Mechanism of Action

Local anesthetics act by decreasing the excitability of nerve cells without affecting the resting potential. Because the action potential, or the ability of nerve cells to be excited, is associated with the movement of Na⁺ across the nerve membranes, anything that interferes with the movement of these ions will interfere with cell excitability. For this reason, many hypotheses have been suggested to explain how local anesthetics regulate the changes in Na⁺ permeability that underlie the nerve impulse. These hypotheses include direct action on ionic channels that interfere with ionic fluxes and interaction with phospholipids and calcium that reduces membrane

flexibility and responsiveness to changes in electrical fields.

The nonspecific membrane actions of local anesthetics can be easily ruled out, because most clinically useful agents, in contrast to general anesthetics, possess a defined set of structure-activity relationships. At much higher drug concentrations, local anesthetics also bind and block K⁺ channels.

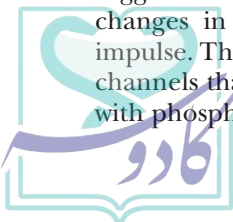
INTERACTION WITH PHOSPHOLIPIDS AND CALCIUM

Calcium exists in the membrane in a bound state. Many investigators believe that the release of the bound calcium is the first step in membrane depolarization and that this release leads to the changes in ionic permeability described previously. It has been suggested that local anesthetics displace the bound calcium from these sites and form more stable bonds, thereby inhibiting ionic fluxes. The following evidence has been offered in support of this theory: Both calcium and local anesthetics bind to phospholipids *in vitro*, reducing their flexibility and responsiveness to changes in electrical fields (56–58). Also, membrane excitability and instability increase in calcium-deficient solutions. Local anesthetics counteract this abnormal increase in excitability, and more local anesthetic is necessary to block excitation in calcium-poor solutions (59). Direct proof of this hypothesis, however, is lacking because of the difficulty in measuring temporal Ca²⁺ movements *in vivo*. It is also possible that the aforementioned cause-and-effect relationship between intracellular free Ca²⁺ and membrane excitability is the result of an Na⁺-Ca²⁺ exchange reaction; that is, the influx of Na⁺ displaces the membrane-bound calcium, which leads to an increase of intracellular free Ca²⁺ and, thereby, increases cellular excitability.

Local anesthetics interact differently, however, with neuronal phospholipids with or without the presence of cholesterol. Thus, the interactions of local anesthetics with the cellular membranes actually may help to explain some of the observed differences in toxicity of the individual local anesthetic agents (60).

ACTION ON VOLTAGE-SENSITIVE SODIUM CHANNELS

As mentioned, the voltage-sensitive Na⁺ channels are membrane-bound glycoproteins that mediate Na⁺ permeability. On excitation, these channels undergo conformational changes from a closed to an open state, thus allowing a rapid influx of sodium. The movement of Na⁺ is blocked by the neurotoxins TTX and STX and by local anesthetics (61). Most electrophysiologists and neuropharmacologists now agree that the mechanism of action of local anesthetics results primarily from their binding to one or more sites within the Na⁺ channels, thus blocking Na⁺ conductance (62). However, the exact location of these binding sites and whether all local anesthetics interact with a common site remain matters of dispute.



ACTION ON SODIUM CONDUCTANCE Local anesthetics block Na^+ conductance by two possible modes of action: tonic inhibition and phasic inhibition (63,64). Tonic inhibition results from the binding of local anesthetics to non-activated closed Na^+ channels and, thus, is independent of channel activation. Phasic inhibition is accomplished when local anesthetics bind to activated, open states (conducting) or to inactivated states (nonconducting) of the Na^+ channels. Thus, it is not surprising that a greater phasic inhibition usually is obtained with repetitive depolarization and is referred to as use-dependent blockade.

Two reasons have been suggested to explain this observation. First, channel inactivation during depolarization increases the number of binding sites that normally are inaccessible to local anesthetics at resting potential. Second, both the open and the inactivated channels possess binding sites with a higher affinity; therefore, local anesthetics bind more tightly and result in a more stable nerve block.

Furthermore, it is generally agreed that most of the clinically useful local anesthetics exert their actions by binding to the inactivated forms of the channels and, thus, prevent their transition to the original resting state (64). Because most of these drugs exhibit both tonic and phasic inhibitions, whether tonic and phasic block results from drug interaction at the same or different sites remains unclear.

LOCAL ANESTHETICS BINDING TO SODIUM CHANNELS Most of the clinically useful local anesthetics are tertiary amines with a pK_a of 7.0 to 9.0. Thus, under physiologic conditions, both protonated forms (onium ions) and the un-ionized, molecular forms are available for binding to the channel proteins. In fact, the ratio between the onium ions $[\text{BH}^+]$ and the un-ionized molecules $[\text{B}]$ can be easily calculated based on the pH of the medium and the pK_a of the drug molecule by the Henderson-Hasselbalch equation:

$$\text{pH} = \text{pK}_a - \log [\text{BH}^+]/[\text{B}]$$

The effect of pH changes on the potency of local anesthetics has been extensively investigated (65). Based on these studies, it was concluded that local anesthetics block the action potential by first penetrating the nerve membrane in their un-ionized forms and then binding to a site within the channels in their onium forms. Perhaps the most direct support for this hypothesis comes from the experimental results of Narahashi et al. (66,67), who studied the effects of internal and external perfusion of local anesthetics (both tertiary amines and quaternary ammonium compounds), at different pH values, on the Na^+ conductance of the squid giant axon. The observation that both tertiary amines and quaternary ammonium compounds produce greater nerve blockage when applied internally indicates an axoplasmic site of action for these compounds.

Furthermore, only the tertiary amines exhibit a reduction in their local anesthetic activities when the internal pH is raised from 7.0 to 8.0. Because the increase of internal pH to 8.0 favors the existence of the un-ionized

forms, this result again suggests that the onium ions are required for binding to the channel receptors. Narahashi and Frazier (68) further estimated that approximately 90% of the blocking actions of lidocaine can be attributed to onium forms of the drug molecule, whereas only approximately 10% can result from un-ionized molecule and, perhaps, at a hydrophobic binding site other than the primary binding site. Benzocaine, because of its lack of a basic amine group ($\text{pK}_a = 2.78$), and other neutral anesthetics, such as benzyl alcohol, have been suggested to bind to this hydrophobic binding site.

In 1984, Hille (69) proposed a unified theory involving a single binding site in the Na^+ channels for both onium ions (protonated tertiary amines and quaternary ammonium compounds) and un-ionized forms of local anesthetics. As depicted in Figure 16.14, a number of pathways are available, depending on the size, pK_a , and lipid solubility of the drug molecules as well as the voltage and frequency-dependent modulation of the channel states, for a drug to reach its binding sites. Protonated anesthetic molecules $[\text{BH}^+]$ and quaternary ammonium compounds reach their target sites via the hydrophilic pathway externally (pathway b in Fig. 16.14), which is available only during channel activation.

The lipid-soluble anesthetic molecules, on the other hand, diffuse across the neuronal membrane in their un-ionized forms. They can interact with the same binding sites from either the hydrophilic pathway (pathway b' in Fig. 16.14) on reprotonation to their onium ions $[\text{BH}^+]$ or via the hydrophobic pathway (pathway a in Fig. 16.14) in their un-ionized forms $[\text{B}]$. Benzocaine and other nonbasic local anesthetic molecules use this hydrophobic pathway and, thus, bind in the hydrophobic domain to produce their actions. Site-directed mutagenesis studies (70–73) suggest that local anesthetics bind to the hydrophobic amino acid residues near the center and the intracellular end of the S6 segment in the domain

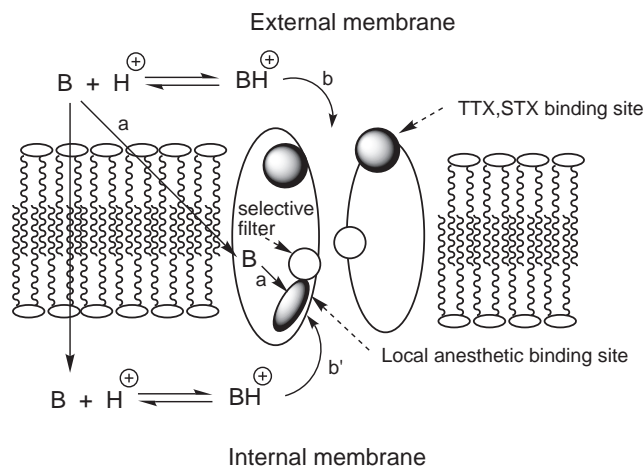
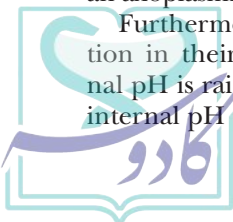


FIGURE 16.14 Model of a sodium channel, as suggested by Hille (69), depicting a hydrophilic pathway (denoted by b and b') and a hydrophobic pathway (denoted by a) by which local anesthetics can reach their binding sites.



D4, whereas the BTX receptor is within segment S6 in domain D1 of the α subunit of the Na^+ channels (Fig. 16.14) (49).

Structure–Activity Relationships

A quick perusal of Table 16.9 reveals that many diverse chemical structures possess local anesthetic properties: amino esters (procaine analogs), amino amides (lidocaine analogs), amino ethers (pramoxine), amino ketones (dyclonine), alcohols (benzyl alcohol and menthol), and phenols (eugenol and phenol). Although it would seem that there is no obvious structure–activity relationship among these agents, most of the clinically useful local anesthetics are tertiary amines with $\text{p}K_a$ values of 7.0 to 9.0. These compounds exhibit their local anesthetic properties by virtue of the interactions of the onium ions with a selective binding site within the Na^+ channels (Fig. 16.14). For this reason, any structural modifications that alter the lipid solubility, $\text{p}K_a$, and metabolic inactivation have a pronounced effect on the ability of a drug molecule to reach or interact with the hypothetical binding sites, thus modifying its local anesthetic properties.

LIPHILIC PORTION The lipophilic portion of the molecule is essential for local anesthetic activity. For most of the clinically useful local anesthetics, this portion of the molecule consists of either an aromatic group directly attached to a carbonyl function (the amino ester series) or a 2,6-dimethylphenyl group attached to a carbonyl function through an $-\text{NH}-$ group (the amino amide series) (Fig. 16.15). Both groups are highly lipophilic

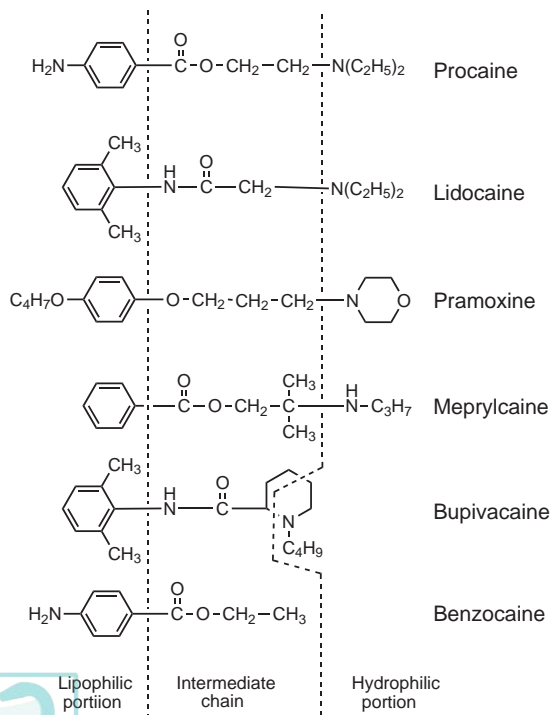
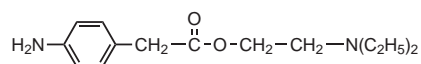


FIGURE 16.15 Structure–activity relationship comparison of local anesthetics.

and appear to play an important role in the binding of local anesthetics to the channel proteins. Structural modification of this portion of the molecule has a profound effect on its physical and chemical properties, which in turn alters its local anesthetic properties.

In the amino ester series, an electron-donating substituent in the *ortho* or *para* (or both) positions increases local anesthetic potency. Such groups as an aromatic amino (procaine, chlorprocaine, and propoxycaine), an alkylamino (tetracaine), or an alkoxy (proparacaine and propoxycaine) group contribute electron density to the aromatic ring by both resonance and inductive effects, thereby enhancing local anesthetic potency over nonsubstituted analogs (e.g., meprylcaine).

As illustrated in Figure 16.16, resonance is expected to give rise to a zwitterionic form (i.e., the electrons from the amino group can be resonance delocalized onto the carbonyl oxygen). Although neither drawn structure of procaine in Figure 16.16 can accurately represent the structure of procaine when it interacts with the local anesthetic binding site, it is reasonable to assume that the greater the resemblance to the zwitterionic form, the greater the affinity for the binding site (i.e., binding from both the hydrophilic pathway b' and hydrophobic pathway a in Fig. 16.14). This is particularly true for the affinity of benzocaine for its binding site, because it lacks a basic amine group. Therefore, it can only bind from the hydrophobic pathway a . Thus, addition of any aromatic substitution that can enhance the formation of the resonance form through electron donation or inductive effects will produce more potent local anesthetic agents. Electron-withdrawing groups, such as nitro ($-\text{NO}_2$), reduce the local anesthetic activity.



Insertion of a methylene group between the aromatic moiety and the carbonyl function as shown above in the procaine molecule, which prohibits the formation of the zwitterionic form, has led to a procaine analog with greatly reduced anesthetic potency. This observation lends further support for the involvement of the resonance form when an ester-type local anesthetic binds to the binding

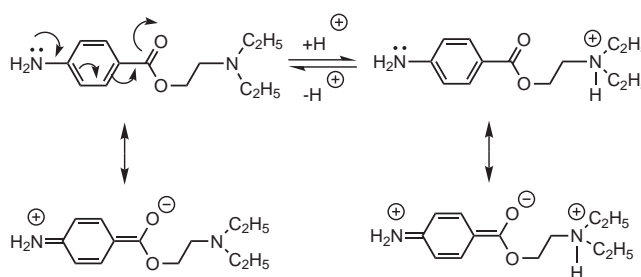


FIGURE 16.16 Possible zwitterionic forms for procaine.

site. When an amino or an alkoxy group is attached to the *meta* position of the aromatic ring, however, no resonance delocalization of their electrons is possible. The addition of this function only increases (alkoxy group) or decreases (amino group) the lipophilicity of the molecule (e.g., benoxinate, $\log D_{\text{pH } 7.4} = 3.19$; and proparacaine, $\log D_{\text{pH } 7.4} = 2.05$).

Furthermore, tetracaine is approximately 50-fold more potent than procaine. Experimentally, this increase in potency cannot be correlated solely with the 2,500-fold increase of lipid solubility by the *n*-butyl group ($\log D_{\text{pH } 7.4} = 2.73$ vs. procaine $\log D_{\text{pH } 7.4} = -0.32$). Perhaps part of this potentiation of local anesthetic activity can be attributed to the electron-releasing property of the *n*-butyl group via the inductive effect, which indirectly enhances the electron density of the *p*-amino group, which in turn increases the formation of the zwitterionic form available for interaction with the binding site proteins via both the hydrophobic and the hydrophilic pathways of the receptor.

Another important aspect of aromatic substitution has been observed from structure–activity relationship studies. In the amino amides (lidocaine analogs), the *o,o'*-dimethyl groups are required to provide suitable protection from amide hydrolysis to ensure a desirable duration of action. Similar conclusions can be made to rationalize the increase in the duration of action of propoxycaine by the *o*-propoxy group. The shorter duration of action, however, observed with chlorprocaine when compared with that of procaine can only be explained by the inductive effect of the *o*-chloro group, which pulls the electron density away from the carbonyl function, thus making it more susceptible to nucleophilic attack by the plasma cholinesterases.

INTERMEDIATE CHAIN The intermediate chain almost always contains a short alkyl chain of one to three carbons in length linked to the aromatic ring via several possible organic functional groups. The nature of this intermediate chain determines the chemical stability of the drug, which also influences the duration of action and relative toxicity. In general, amino amides are more resistant to metabolic hydrolysis than the amino esters and, thus, have a longer duration of action. The placement of small alkyl groups (i.e., branching), especially around the ester function (e.g., meprylcaine) or the amide function (e.g., bupivacaine, etidocaine, prilocaine, or ropivacaine), also hinders esterase- or amidase-catalyzed hydrolysis, prolonging the duration of action (Fig. 16.15 and Table 16.9). It should be mentioned, however, that prolonging the duration of action of a compound usually increases its systemic toxicities unless it is more selective toward the voltage-gated Na^+ channel, as in the case of levobupivacaine (74,75).

In the lidocaine series, lengthening of the alkyl chain from one to two or three increases the pK_a of the terminal tertiary amino group from 7.7 to 9.0 or 9.5, respectively. Thus, lengthening of the intermediate chain effectively

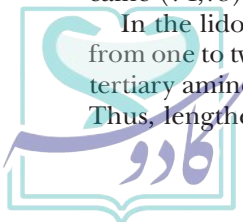
reduces local anesthetic potency as a result of a reduction of onium ions under physiologic conditions. As mentioned earlier, the onium ions are required for effective binding of the amino amide–type local anesthetics to the channel binding sites.

HYDROPHILIC PORTION Most clinically useful local anesthetics have a tertiary alkylamine, which readily forms water-soluble salts with mineral acids, and this portion is commonly considered to be the hydrophilic portion of the molecule (Fig. 16.9). The necessity of this portion of the molecule for amino ester–type local anesthetics remains a matter of debate. The strongest opposition for requiring a basic amino group for local anesthetic action comes from the observation that benzocaine, which lacks the basic aliphatic amine function, has potent local anesthetic activity. For this reason, it is often suggested that the tertiary amine function in procaine analogs is needed only for the formation of water-soluble salts suitable for pharmaceutical preparations. With the understanding of the voltage-activated Na^+ channel and the possible mechanism of action of local anesthetics previously discussed, however, it is quite conceivable that the onium ions produced by protonation of the tertiary amine group are also required for binding in the voltage-gated Na^+ channels (Fig. 16.14).

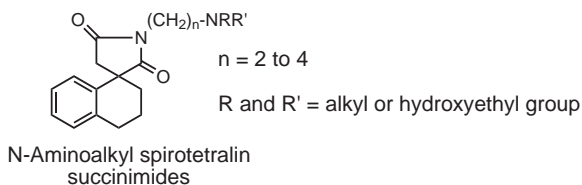
From Table 16.9, the hydrophilic group in most of the clinically useful drugs can be in the form of a secondary or tertiary alkyl amine or part of a nitrogen heterocycle (e.g., pyrrolidine, piperidine, or morpholine). As mentioned earlier, most of the clinically useful local anesthetics have pK_a values of 7.5 to 9.0. The effects of an alkyl substituent on the pK_a depend on the size, length, and hydrophobicity of the group; and thus, it is difficult to see a clear structure–activity relationship among these structures. It is generally accepted that local anesthetics with higher lipid solubility and lower pK_a values appear to exhibit more rapid onset and lower toxicity.

Stereochemistry

Are there any stereochemical requirements of local anesthetic compounds when they interact with the Na^+ channel binding sites? A number of clinically used local anesthetics do contain a chiral center (i.e., bupivacaine, etidocaine, mepivacaine, and prilocaine) (Table 16.9), but in contrast to other classes of drugs (e.g., cholinergics), the effect of optical isomerism on isolated nerve preparations revealed a lack of stereospecificity. In a few cases (e.g., prilocaine, bupivacaine, and etidocaine), however, small differences in the total pharmacologic profile of optical isomers have been noted when administered in vivo (76–78). Whether these differences result from differences in uptake, distribution, and metabolism or from direct binding to the Na^+ channel have not been determined. When structural rigidity has been imposed on the molecule, however, as in the case of some aminoalkyl spirotrietralin succinimides (79), differences in local anesthetic potency of the enantiomers have been observed (range, 1:2 to 1:10). Although these differences in enantiomers



clearly are not as pronounced as those with other pharmacologic agents, such as adrenergic antagonists or anticholinergic drugs, steric requirements are necessary for effective interaction between a local anesthetic agent and its proposed channel binding sites.



Stereochemistry of the local anesthetics, however, plays an important role in their observed toxicity and pharmacokinetic properties. For example, ropivacaine and levobupivacaine, the only optically active local anesthetics currently being marketed, have considerably lower cardiac toxicities than their close structural analog, bupivacaine (80). Furthermore, the degree of separation between motor and sensory blockade is more apparent with ropivacaine and levobupivacaine relative to bupivacaine at a lower end of the dosage scale (81). Thus, the observed cardiac toxicity of bupivacaine has been attributed to the *R*(+)-bupivacaine enantiomer (76–78). The exact mechanisms for this enantiomeric difference remain unknown. Longobardo and colleagues observed a stereoselective blockade on the cardiac hKv1.5 channels by the *R*(+)-enantiomers of bupivacaine, ropivacaine, and mepivacaine (82,83). It should be noted that *S*(-)-bupivacaine, which is approved by the U.S. Food and Drug Administration and marketed under the name of Chirocaine, has even less CNS toxicity than ropivacaine.

Metabolism of Local Anesthetics

An understanding of the metabolism of local anesthetics is important in clinical practice because the overall toxicity of a drug depends not only on its uptake and tissue distribution but also on how it is deactivated *in vivo*. The amino ester-type local anesthetics are rapidly hydrolyzed by plasma cholinesterase (also known as pseudocholinesterase), which is widely distributed in body tissues. These compounds can therefore be metabolized in the blood, kidneys, and liver and, to a lesser extent, at the site of administration. For example, both procaine and benzocaine are easily hydrolyzed by cholinesterase into PABA and the corresponding *N,N*-diethylaminoethyl alcohol.

It is not surprising that potential drug interactions exist between the amino ester-type local anesthetics and other clinically important drugs, such as cholinesterase inhibitors or atropine-like anticholinergic drugs (see Chapter 9). These compounds either inhibit or compete with local anesthetics for cholinesterases, therefore prolonging local anesthetic activity and/or toxicity. Another potential drug interaction with clinical significance can be envisioned between benzocaine and sulfonamides; that is, the hydrolysis of benzocaine to PABA can antagonize the antibacterial activity of sulfonamides.

The amino amide-type local anesthetics, however, are metabolized primarily in the liver, involving CYP1A2 isozymes (84). A general metabolic scheme for lidocaine is shown in Figure 16.17.

Marked species variations occur in the quantitative urinary excretion of these metabolites. For example, rats produce large quantities of the 3-hydroxy derivatives of both lidocaine and monoethylglycinexylidide, which are subsequently conjugated and recycled in the bile. Significant quantities of these two metabolites, however, are not produced by guinea pigs, dogs, or humans. Therefore, it is unlikely that biliary excretion is a major pathway for excretion in humans. Species variability is important primarily when the acute and chronic toxicity of nonester-type local anesthetic agents is being evaluated.

Although the exact mechanism for the CNS toxicity of lidocaine remains unclear, the metabolic studies of lidocaine provide some insight for future studies. Of all the metabolites of lidocaine, only monoethylglycinexylidide (and not glycinexylidide) contributes to some of the CNS side effects of lidocaine. This observation suggests that the toxicities of lidocaine are, perhaps, related to the

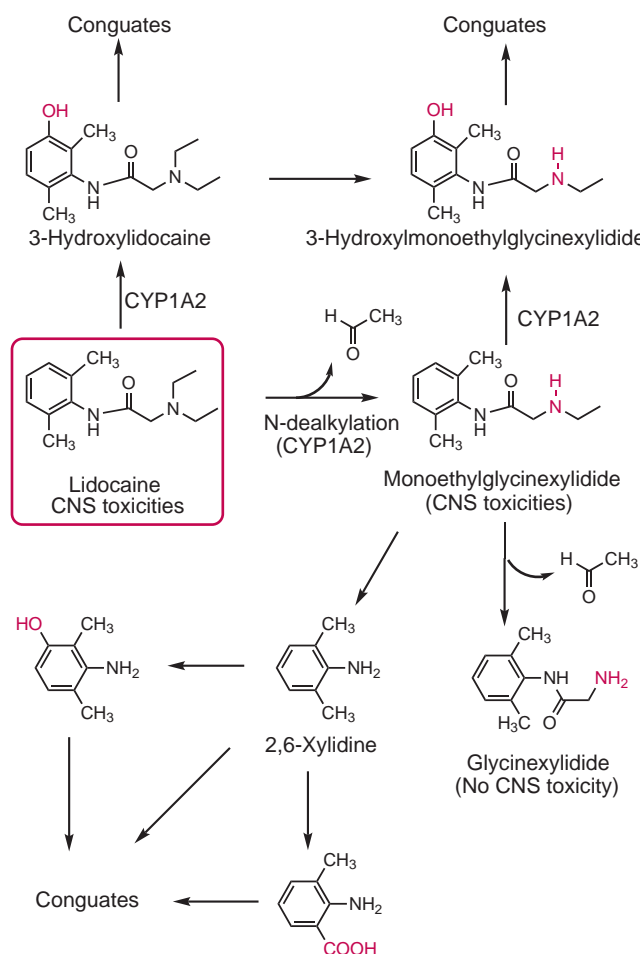
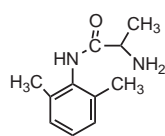
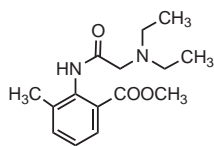


FIGURE 16.17 Metabolic scheme for lidocaine.

removal of the *N*-ethyl groups of lidocaine after crossing the blood–brain barrier. Support for this hypothesis can be obtained from the fact that reaction of a tryptophan derivative with formaldehyde under physiologic conditions gives rise to a β -carboline derivative, which is a CNS convulsant (Fig. 16.18). Advances in the GABA_A receptor–benzodiazepine receptor–chloride ion channels and their role in the mechanism of action of benzodiazepine anticonvulsants lends further support to this hypothesis (i.e., many β -carbolines are inverse agonists at the benzodiazepine binding site).



Tocainide



Tolycaine

To minimize these unwanted side effects of lidocaine, tocainide and tolycaine have been prepared and found to possess good local anesthetic activity without any appreciable CNS side effects. Tocainide, which lacks the vulnerable *N*-ethyl group but has an α -methyl group to prevent degradation of the primary amine group from amine oxidase, has desirable local anesthetic properties. Tolycaine has an *o*-carbomethoxy substituted for one of the *o*-methyl groups of lidocaine. The carbomethoxy group is fairly stable in tissues but is rapidly hydrolyzed in the blood to the polar carboxylate group and, thus, is unable to cross the blood–brain barrier.

For this reason, tolycaine lacks any CNS side effects, even though it still contains the *N*-ethyl group. It should be noted, however, that both tocainide and tolycaine are primarily used clinically as antiarrhythmic agents.

Furthermore, the metabolism of nonester-type drugs, especially lidocaine derivatives, is also known to be more

prone to being influenced by enzyme induction or inhibition due to other coadministered medications (e.g., cimetidine and barbiturates).

Common Agents Used for Local Anesthesia

Local anesthetics are widely used in many primary care settings. Techniques for their administration in these settings include topical application, local infiltration, field block, and peripheral nerve block. Their use can be maximized by an understanding of their potencies, durations of action, routes of administration, and pharmacokinetic and side effect profiles. The generic name, trade name, and recommended application are given in Table 16.8, and the chemical structures of these agents can be found in Table 16.9.

Articaine

Articaine (Table 16.9) has been widely used in dentistry since its U.S. Food and Drug Administration approval in 2000 due to its quick onset and short duration of action. The structure of articaine differs from the structures of all other amino amide-type local anesthetics in that it contains the bioisosteric thiophene ring instead of a benzene ring and a carbomethoxy group. This renders the molecule more lipophilic and, thus, makes it easier to cross lipoidal membranes.

Its local anesthetic potency is approximately 1.5-fold that of lidocaine, even though it has similar pK_a (7.8) and smaller $\log D_{pH\ 7.4}$ (1.65 vs. $\log D_{pH\ 7.4}$ of 2.26 for lidocaine) and plasma protein binding (76%) properties. Articaine is metabolized primarily by plasma cholinesterases because of the presence of an ester group and, therefore, has a much shorter duration of action than lidocaine (i.e., only approximately one-fourth that of lidocaine). Articaine undergoes rapid hydrolysis of the carbomethoxy group to give articainic acid, which is eliminated either unchanged (75%) or as its glucuronides (25%). Compared with other short-acting, amino amide-type local anesthetics, such as mepivacaine, lidocaine, or prilocaine, articaine is said to be a much safer drug for regional anesthesia and is the drug of choice for dental procedures.

Benzocaine

Benzocaine (Table 16.9) is used topically by itself or in combination with menthol or phenol in nonprescription dosage forms such as gels, creams, ointments, lotions, aerosols, and lozenges to relieve pain or irritation caused by such conditions as sunburn, insect bites, toothache, teething, cold sores or canker sores in or around the mouth, and fever blisters. Benzocaine is a lipophilic local anesthetic agent with a short duration of action.

Like most amino ester-type local anesthetics, it is easily hydrolyzed by plasma cholinesterase. However, because of its low pK_a , it is un-ionized under most physiologic conditions and, therefore, can only bind to the lipid site in the sodium channel ($\log D_{pH\ 7.4} = 1.91$) (Fig. 16.14). When administered topically to abraded skin, it

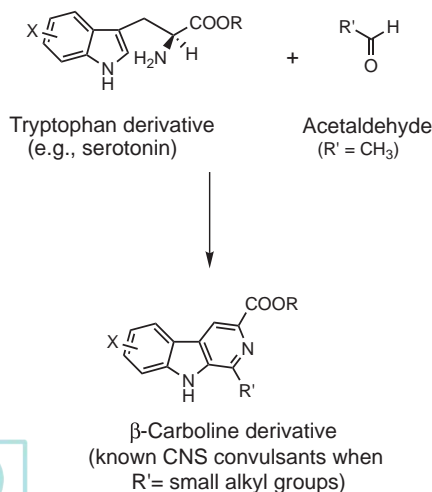


FIGURE 16.18 Reaction of a tryptophan derivative with acetaldehyde under physiologic conditions.

can easily cross membranes into the systemic circulation to cause systemic toxicities. Furthermore, being a PABA derivative, it has similar allergenic properties to procaine and is contraindicated with sulfonamide antibacterial agents.

Bupivacaine and Levobupivacaine

Bupivacaine hydrochloride (Table 16.8) is a racemic mixture of the *S*(-)- and *R*(+)-enantiomers. Bupivacaine has higher lipid solubility ($\log D_{\text{pH } 7.4} = 2.54$) and a much decreased rate of hepatic degradation compared with lidocaine. For this reason, bupivacaine has significantly greater tendency than lidocaine to produce cardiotoxicity. Because of its greater affinity for voltage-gated Na^+ channels, the *R*(+)-enantiomer confers greater cardiotoxicity than racemic bupivacaine.

It was not surprising to see the approval of levobupivacaine, the *S*(-)-enantiomer of (\pm)-bupivacaine, as the second optically active, amino amide-type local anesthetic for parenteral applications. Like ropivacaine, levobupivacaine has a lower cardiotoxicity than bupivacaine, but it also has a lower CNS toxicity than both ropivacaine and lidocaine.

Possible pathways for metabolism of bupivacaine include CYP1A2 aromatic 3-hydroxylation, CYP3A4 *N*-dealkylation, and to a minor extent, the amide hydrolysis. Only the *N*-dealkylated product, however, has been identified in urine after epidural or spinal anesthesia.

Chloroprocaine

Chloroprocaine (Fig. 16.8) is a very short-acting, amino ester-type local anesthetic used to provide regional anesthesia by infiltration as well as by peripheral and central nerve block, including lumbar and caudal epidural blocks. The presence of a chlorine atom *ortho* to the carbonyl of the ester function increases its lipophilicity ($\log D_{\text{pH } 7.4} = 0.95$) and its rate of hydrolysis by plasma cholinesterase at least threefold compared to procaine and benzocaine. Thus, chloroprocaine can be used in maternal and neonatal patients with minimal placental passage of chloroprocaine. The lower plasma cholinesterase activity in the maternal epidural space must still have sufficient activity for degrading chloroprocaine and, thus, not allowing it to cross the placental barrier. Like PABA, the hydrolysis product of chloroprocaine, 4-amino-2-chlorobenzoic acid, also inhibits the action of sulfonamides. Therefore, its use with sulfonamides should be avoided.

Lidocaine

Lidocaine (Fig. 16.8) is the most commonly used amino amide-type local anesthetic. Lidocaine is very lipid soluble ($\log D_{\text{pH } 7.4} = 2.26$) and, thus, has a more rapid onset and a longer duration of action than most amino ester-type local anesthetics, such as procaine and tetracaine. It can be administered parenterally (with or without epinephrine) or topically either by itself or in combination

with prilocaine or etidocaine as a eutectic mixture that is very popular with pediatric patients. The use of lidocaine–epinephrine mixtures should be avoided, however, in the areas with limited vascular supply to prevent tissue necrosis. Lidocaine is also frequently used as a class IB antiarrhythmic agent for the treatment of ventricular arrhythmias, both because it binds and inhibits Na^+ channels in the cardiac muscle and because of its longer duration of action than amino ester-type local anesthetics (Chapter 21).

CNS changes are the most frequently observed systemic toxicities of lidocaine. The initial manifestations are restlessness, vertigo, tinnitus, slurred speech, and eventually, seizures. Subsequent manifestations include CNS depression with a cessation of convulsions and the onset of unconsciousness and respiratory depression or cardiac arrest. This biphasic effect occurs because local anesthetics initially block the inhibitory GABAergic pathways, resulting in stimulation, and eventually block both inhibitory and excitatory pathways (i.e., block the Na^+ channels associated with the NMDA receptors, resulting in overall CNS inhibition) (85).

Lidocaine is extensively metabolized in the liver by CYP3A4 *N*-dealkylation and aromatic hydroxylation catalyzed by CYP1A2 (Fig. 16.17). Lidocaine also possesses a weak inhibitory activity toward the CYP1A2 isozymes and, therefore, can interfere with metabolism of other medications (86).

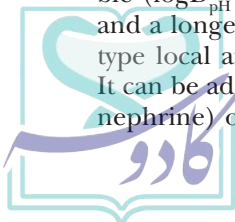
Mepivacaine

Mepivacaine hydrochloride (Fig. 16.8) is an amino amide-type local anesthetic agent widely used to provide regional analgesia and anesthesia by local infiltration, peripheral nerve block, and epidural and caudal blocks. The pharmacologic and toxicologic profile of mepivacaine is quite similar to that of lidocaine, except that mepivacaine is less lipophilic ($\log D_{\text{pH } 7.4} = 1.95$) and has a slightly longer duration of action but lacks the vasodilator activity of lidocaine. For this reason, it serves as an alternate choice for lidocaine when addition of epinephrine is not recommended in patients with hypertensive vascular disease.

Mepivacaine undergoes extensive hepatic metabolism catalyzed by CYP3A4 and CYP1A2, with only a small percentage of the administered dosage (<10%) being excreted unchanged in the urine. The major metabolic biotransformations of mepivacaine are *N*-dealkylation (to give the *N*-demethylated compound 2',6'-pipecoloxylidide) and aromatic hydroxylations. These metabolites are excreted as their corresponding glucuronides.

Ropivacaine

S-Ropivacaine hydrochloride (Fig. 16.8) is the first optically active, amino amide-type local anesthetic marketed in recent years. It combines the anesthetic potency and long duration of action of (\pm)-bupivacaine with a side effect profile intermediate between those of



SCENARIO: OUTCOME AND ANALYSIS

Outcome

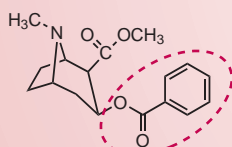
Paul Arpino

After consulting with the covering pharmacist and the hospital's allergy specialist, the team decides to proceed with the type of anesthesia and surgery as planned. On the day of the surgery, CDL received the peripheral nerve block with ropivacaine and required minimal adjunctive medications during the procedure. Postoperatively, CDL's pain was well controlled and there was no evidence of an allergic reaction.

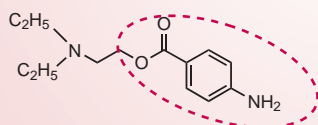
Chemical Analysis

S. William Zito and Victoria Roche

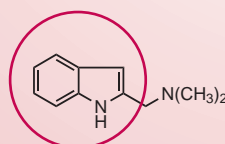
Procaine is a local anesthetic developed from the investigation of cocaine analogs that were synthesized in an effort to enhance the local anesthetic properties and reduce cocaine's addiction and acute toxicity liability. Cocaine and procaine are benzoic acid derivatives and both are known to cause allergic reactions.



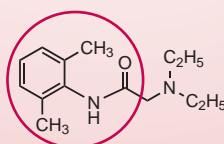
Cocaine



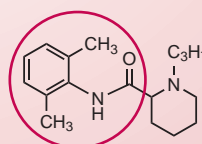
Procaine



Isogramine



Lidocaine



Ropivacaine

The aminoalkyl side chain is not necessary for local anesthetic activity but is useful for forming water-soluble salts for parenteral administration. The para-amino phenyl substituent enhances local anesthetic effect by increasing the electron density of the carbonyl oxygen through electron induction.

Ropivacaine is a local anesthetic developed from another natural alkaloid, isogramine. Structure activity studies of isogramine led to the development of the lidocaine class (anilides) of local anesthetics.

The lidocaine types of local anesthetics are bioisosteres of isogramine. The amino alkyl side chain serves to form water-soluble salts for parenteral administration. As anilides, these compounds have a longer duration of action compared with the benzoic acid ester class, and the 2,6-dimethyls of the aromatic ring also serve to increase duration of action.

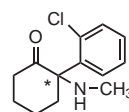
This class of local anesthetics is less irritating upon injection and, most importantly for this case, have no cross-allergic sensitivity with the benzoic acid class of local anesthetics. General anesthesia must be avoided in this case because it suppresses upper airway muscle activity, and it may impair breathing by allowing the airway to close. General anesthesia thus may increase the number of and duration of sleep apnea episodes of this patient.

CASE STUDY

S. William Zito and Victoria Roche

BB is a 19-year-old pregnant woman in her second trimester. Until now she has had an unremarkable pregnancy. However, today she presents to the emergency department complaining of 3 days of right lower quadrant pain, anorexia, and persistent nausea and vomiting. A physical examination of BB revealed vital signs of blood pressure, 127/68 mm Hg; heart rate, 86 beats per minute; respiratory rate, 18 breaths per minute, and a temperature of 97.5 °F. A diagnosis is made of acute appendicitis and surgery is recommended. Preoperative testing showed slight leucocytosis with a white blood cell count of 12,000/mm³; her hemoglobin was 12.1 gm/dL, with a hematocrit level of 34.9% and platelet count of 306,000/mm³. BB's medical history was unexceptional; she has had no previous health issues and she is not taking any medications except for prenatal multivitamins, which contain folic acid and iron. She reports no surgical history and that her parents have had operations for which, to her knowledge, there were no anesthetic sequelae. The surgical trauma team expects the operation to take 45 minutes and plans to

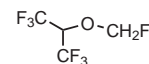
use general anesthesia using rapid induction and securing her airway with a small cuffed endotracheal tube. The following three general anesthetics are proposed. Which one would you recommend?



1



2



3

1. Conduct a thorough and mechanistic SAR analysis of the three therapeutic options in the case.
2. Apply the chemical understanding gained from the SAR analysis to this patient's specific needs to make a therapeutic recommendation.

bupivacaine and lidocaine. Although ropivacaine has a pK_a nearly identical to that of bupivacaine, it is two- to threefold less lipid soluble ($\log D_{pH\ 7.4} = 2.06$) and has a smaller volume of distribution, a greater clearance, and a shorter elimination half-life than bupivacaine in humans.

The metabolism of ropivacaine in humans is mediated by hepatic CYP1A2 and, to a minor extent, by CYP3A4 (87). The major metabolite is 3-hydroxyropivacaine, and the minor metabolite is *S*-2',6'-pipecoloxylidide (an *N*-dealkylated product).

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