Chapter 2

Drugs Affecting Peripheral Nervous System

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I. INTRODUCTION TO THE PERIPHERAL EFFERENT NERVOUS SYSTEM

A. **The somatic nervous system innervates skeletal muscle** and controls motor functions of the body. Axons originate from the spinal cord and release the neurotransmitter acetylcholine (ACh) at the neuromuscular junction. Some drugs can affect both the somatic and the autonomic nervous systems because ACh is a transmitter in both systems.

B. **The autonomic nervous system** regulates the activity of the **heart, secretory cells, and smooth muscle.** Two neurons are involved in the transmission process. The first neuron originates in the central nervous system (CNS) and synapses in a ganglion outside the CNS. A second neuron then innervates the target (effector) tissue.

1. **Organization** (Figure 2-1)
   a. **Sympathetic nervous system**
      (1) **Preganglionic neurons** originate from the thoracic and lumbar portions of the spinal cord and terminate in the para- or post-vertebral ganglia, or they directly innervate the adrenal medulla. Functionally, the adrenal medulla responds as if it were a ganglion.
      (2) **Postganglionic neurons** originate from the ganglia and innervate the effector cell.
   b. **Parasympathetic nervous system**
      (1) **Preganglionic neurons** originate from either the midbrain, the medulla oblongata, or the sacral portion of the spinal cord. They terminate on postganglionic neurons. The terminals of the preganglionic neurons and ganglia are located in or close to the effector cell.
      (2) **Postganglionic neurons** innervate the tissue.
2. **Neurotransmitters** are chemical substances that transmit impulses across junctions such as synapses (e.g., nerve-to-nerve, nerve-to-effector cell).
   a. **Sympathetic nervous system**
      (1) **Preganglionic neurons** release **ACh** onto **nicotinic receptors** of postganglionic neurons or the adrenal medulla.
      (2) **Postganglionic neurons** release **norepinephrine (NE) onto adrenergic receptors (adrenoceptors)** in the effector tissue.
   b. **Parasympathetic nervous system**
      (1) **Preganglionic neurons** release **ACh** onto **nicotinic receptors** of postganglionic neurons.
      (2) **Postganglionic neurons** release **ACh** onto **muscarinic receptors** in the effector cell.
3. **Receptors** (Table 2-1)
   a. **Cholinergic receptors** mediate the effects of **ACh**. They are muscarinic or nicotinic, named after plant alkaloids responsible for the physiologic effects of poisonous mushrooms and tobacco, respectively.
      (1) **Muscarinic receptors** have five subtypes, M_1–M_5. M_1 receptors are found in neurons to mediate excitatory postsynaptic potential (EPSP); M_2 receptors are found in the heart (to decrease excitability); M_3 receptors are found in smooth muscles, sphincters, and secretory glands; M_4 receptors are found in the CNS; and M_5 receptors are found in the midbrain dopaminergic neurons [to increase dopamine (DA) release], cerebral arteries and arterioles, possibly peripheral blood vessels, and lymphocytes. M_1, M_3, and M_5 receptors

TABLE 2-1. Tissue Receptors and Response to Stimulation

	Adrenergic		Cholinergic	
Effector Organ	**Receptor Type**	**Response to Stimulation**	**Receptor Type**	**Response to Stimulation**
Heart				
S-A node	$\beta_1 > \beta_2$	↑Heart rate	M_2	↓Heart rate
Atria	$\beta_1 > \beta_2$	↑Contractility ↑Conduction velocity	M_2	↓Contractility
A-V node	$\beta_1 > \beta_2$	↑Automaticity ↑Conduction velocity	M_2	↓Conduction velocity A-V block
Ventricles	$\beta_1 > \beta_2$	↑Contractility ↑Conduction velocity ↑Automaticity	M_2	↓Contractility
His-Purkinje system	$\beta_1 > \beta_2$	↑Conduction velocity ↑Automaticity	—	—
Arteries				
Coronary	α_1, α_2 β_2	Constriction Dilation	M_3^*	Dilation
Renal	α_1, α_2 β_1, β_2	Constriction Dilation	M_3^*	Dilation
Skin and mucosa	α_1, α_2	Constriction	M_3^*	Dilation
Skeletal muscle	α_1 β_2	Constriction Dilation	M_3^*	Dilation
Pulmonary	α_1 β_2	Constriction Dilation	M_3^*	Dilation
Abdominal viscera	α_1 β_2	Constriction Dilation	M_3^*	Dilation
Veins	α_1, α_2 β_2	Constriction Dilation	—	—
Endothelium	—.	—	M_3	↑ NO synthesis
Eye				
Iris				
Radial muscle	α_1	Contraction (mydriasis)	—	—
Sphincter muscle	—	—	M_3	Contraction (miosis)
Ciliary muscle	β_2	Relaxation (far vision)	M_3	Contraction (near vision)
Salivary glands	α_1	↑ Secretion	M_3	↑ Secretion
Lung				
Tracheal and bronchial smooth muscle	β_2	Relaxation	M_3	Contraction
Bronchial glands	α_2 β_2	↓Secretion ↑Secretion	M_3	↑Secretion
Stomach				
Motility and tone	$\alpha_2, \beta_1, \beta_2$	Decrease	M_3	Increase
Sphincters	α_1	Contraction	M_3	Relaxation
Secretion	α_2	Inhibition	M_3	Stimulation
Intestine				
Motility and tone	$\alpha_2, \beta_1, \beta_2$	Decrease	M_3	Increase
Sphincters	α_1	Contraction	M_3	Relaxation
Secretion	α_2	Inhibition	M_3	Stimulation
Gallbladder and ducts	β_2	Relaxation	M_3	Contraction

TABLE 2-1. (*continued*)

	Adrenergic		Cholinergic	
Effector Organ	**Receptor Type**	**Response to Stimulation**	**Receptor Type**	**Response to Stimulation**
Kidney				
Renin secretion	α_2 β_1	Decrease Increase	—	—
Urinary bladder				
Detrusor	β_2	Relaxation	M_3	Contraction
Trigone and sphincter	α_1	Contraction	M_3	Relaxation
Ureter				
Motility and tone	α_1	Increase	M_3	Increase (?)
Uterus	α_1, α_2 β_2	Pregnant, contraction Nonpregnant, relaxation	M_3	Contraction
Sex organs, male	α_1	Ejaculation	M_3	Erection
Skin				
Pilomotor muscles	α_1	Contraction		
Sweat glands	α_1	↑ Localized secretion (Adrenergic sweating)	M_3	↑Generalized secretion
Spleen capsule	α_1 β_2	Contraction Relaxation	— —	
Adrenal medulla	—		Nicotinic (N_N)	↑Epi, NE secretion
Skeletal muscle	β_2	↑Contractility, Glycogenolysis, K^+ uptake	—	
Liver	α_1, β_2	↑Glycogenolysis	—	—
Pancreas				—
Acini	α_2	↓Secretion	M_3	Secretion
Islets (β cells)	α_2 β_2	↓Secretion ↑Secretion	M_3	Secretion
Fat cells	α_1, β_{1-3}	↑Lipolysis (thermogenesis)	—	—
	α_2	↓lipolysis		
Salivary glands	α_1	↑K^+ and H_2O secretion	M_3	↑K^+ and H_2O secretion
Nasopharyngeal glands	—	—	M_3	↑Secretion
Pineal glands	β	↑Melatonin secretion	—	—
Posterior pituitary	α_2	↓AVP secretion	—	—
Autonomic nerve endings				
Sympathetic				
Autoreceptor	α_2	↓NE release		
Heteroreceptor		—	M_2	↓NE release from sympathetic nerve terminal
Parasympathetic				
Autoreceptor		—	M_2	↓ACh release
Heteroreceptor	α_2	↓ACh release from myenteric plexus		

*These receptors are in endothelium, which respond to ACh by increasing NO synthesis. NO diffuses into muscle and causes vasodilation.

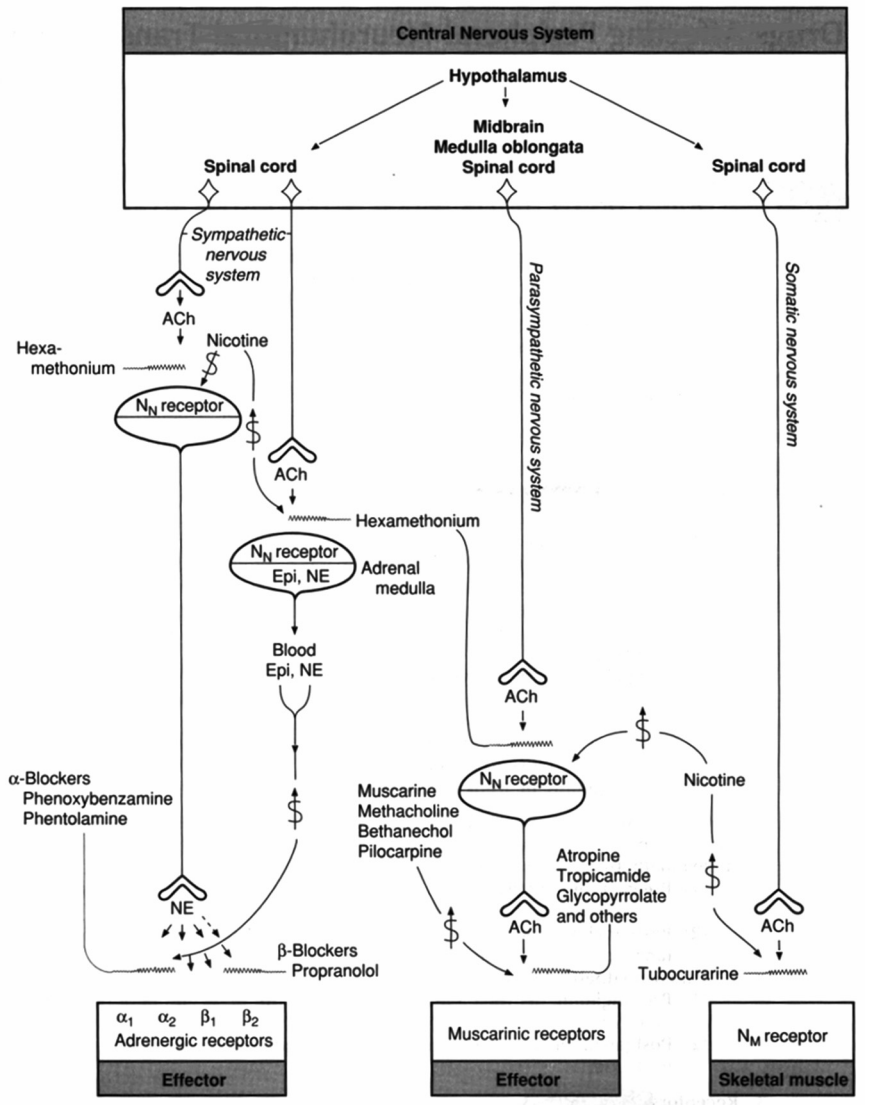


FIGURE 2-1. Effector neurons of the peripheral nervous system. Drugs that stimulate (\$) and block (▁▁▁) receptors are also shown. N_N, ganglionic nicotinic receptor; N_M, skeletal muscle nicotinic receptor; NE, norepinephrine; Epi, epinephrine; ACh, acetylcholine. (From Figure 2-1, *NVMS Pharmacology*.)

are coupled to G_q, whereas M_2 and M_4 receptors are coupled to $G_{i/o}$ (Table 2-2).

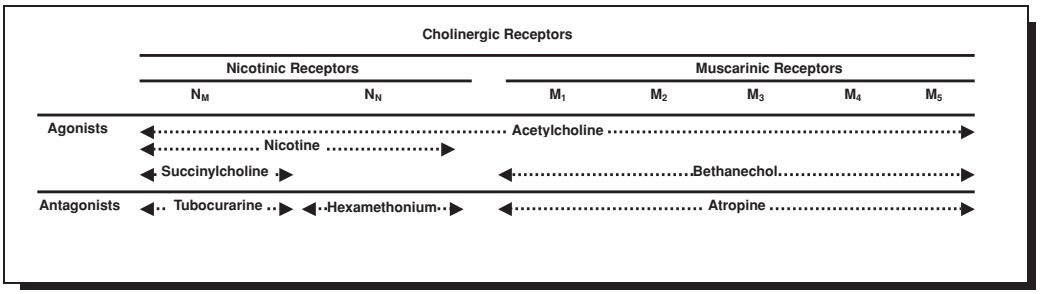
(2) Nicotinic receptors have two subtypes, N_M and N_N. N_M receptors are found in the muscle of neuromuscular junctions, whereas N_N receptors are found in the neurons of the CNS and autonomic ganglia. Nicotinic receptors are part of the nonselective cation channels; activation of these receptors will open the channels to permit the passage of Na^+, K^+, and Ca^{2+}, predominantly Na^+. As a result, membrane is depolarized, which triggers the opening of voltage-dependent Ca^{2+} channels to further increase Ca^{2+} influx.

b. Adrenergic receptors mediate the effects of **NE** and **epinephrine (Epi)**.

(1) α-Receptors: α_1, α_2

These receptors are found in many tissues (Table 2-1). α_2-Receptors are also found in presynaptic site of the adrenergic neuron. α_1-Receptors are coupled to G_q, whereas α_2-receptors are coupled to $G_{i/o}$.

TABLE 2-2. Cholinergic Receptor Pharmacology—An Overview



(2) β-Receptors: $\beta_1, \beta_2, \beta_3$
Both β_1- and β_2-receptors are found in many tissues and elicit many different effects (Table 2-1). β_3-Receptors are found mainly in adipocytes and some in myocardium. All three β-receptor subtypes are coupled to G_s.

II. ADRENERGIC AGONISTS (SYMPATHOMIMETIC AMINES). An overview is presented in Table 2-3.

A. Catecholamines

1. Epi, NE, and DA are endogenous substances that serve as hormones and neurotransmitters. They are also used therapeutically as drugs.

a. Chemistry and biosynthesis are illustrated in Figure 2-2.

b. Mechanism of action (Figure 2-3)

(1) Epi is a potent agonist of all adrenergic receptors (i.e., α_1, α_2, β_1, β_2, and β_3).

(2) NE is a potent agonist of α_1-α_2-, and β_1-receptors. It has little effect on β_2-receptors.

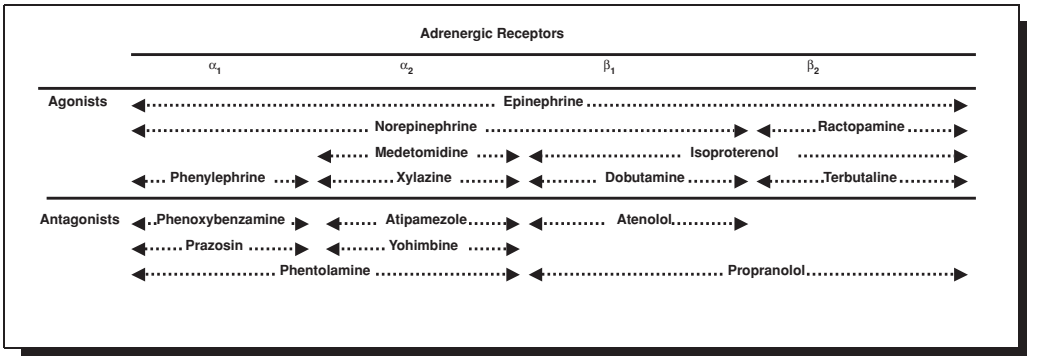
(3) Dopamine

(a) DA causes the release of NE from adrenergic neurons, which activates α_1-and β_1-receptors.

(b) DA activates specific DA receptors.

i. D_1-receptors are present in the **renal, mesenteric, and coronary** circulation and are activated by low concentrations of DA. Activation

TABLE 2-3. Adrenergic Receptor Pharmacology—An Overview



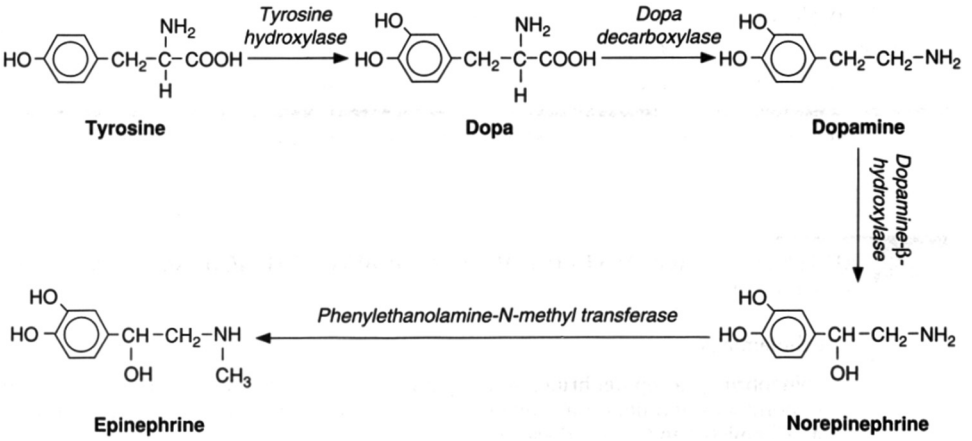


FIGURE 2-2. Biosynthesis of dopamine, norepinephrine, and epinephrine. (From Figure 2-2, *NVMS Pharmacology*.)

of these receptors evokes **vasodilatation**, which is blocked by DA receptor antagonists (e.g., **haloperidol**), but not by β-adrenergic receptor antagonists. **D_1-receptors are coupled to G_s, thereby stimulating cyclic AMP synthesis** (more cyclic AMP, more relaxation of smooth muscle).

ii. **D_2-receptors** are present in **ganglia, adrenal cortex, and certain areas of the CNS**, including the **substantia nigra and pituitary gland**. Activation of these receptors **inhibits neuroendocrine release**. **D_2-receptors are coupled to $G_{i/o}$, thereby inhibiting cyclic AMP synthesis** (less cyclic AMP, less neurosecretion).

iii. **D_3-receptors** are present in the nucleus accumbens located at the base of the striatum. D_3-receptors are coupled to $G_{i/o}$.

iv. **D_4-receptors** are present in the heart and CNS. D_4-receptors are coupled to $G_{i/o}$.

v. **D_5-receptors** are present in lymphocytes, hippocampus, and nucleus accumubens. D_5-receptors are coupled to G_s.

c. Pharmacokinetics

(1) Absorption

(a) **Catecholamines** are poorly absorbed following oral administration, partly because the drugs are rapidly oxidized and conjugated.

(b) They are absorbed from the respiratory tract when nebulized and inhaled.

(c) SC absorption is slow because of vasoconstriction.

(2) Fate

(a) **Distribution.** Catecholamines do not cross the blood–brain barrier readily.

(b) **Deactivation** (see Figure 2-3)

i. **Tissue uptake mechanisms** remove the drug from the receptor site, thereby decreasing the number of receptors being occupied and decreasing the response.

$Uptake_1$ is the active uptake of the drug into the **presynaptic** sympathetic nerve terminal. **Cocaine** produces a sympathomimetic effect by **blocking $uptake_1$**.

$Uptake_2$ is the uptake of catecholamines into the **effector** cell. Effector cell contains monoamine oxidase (**MAO**) and catechol-*O*-methyltransferase (**COMT**), which metabolize catecholamines to inactive products.

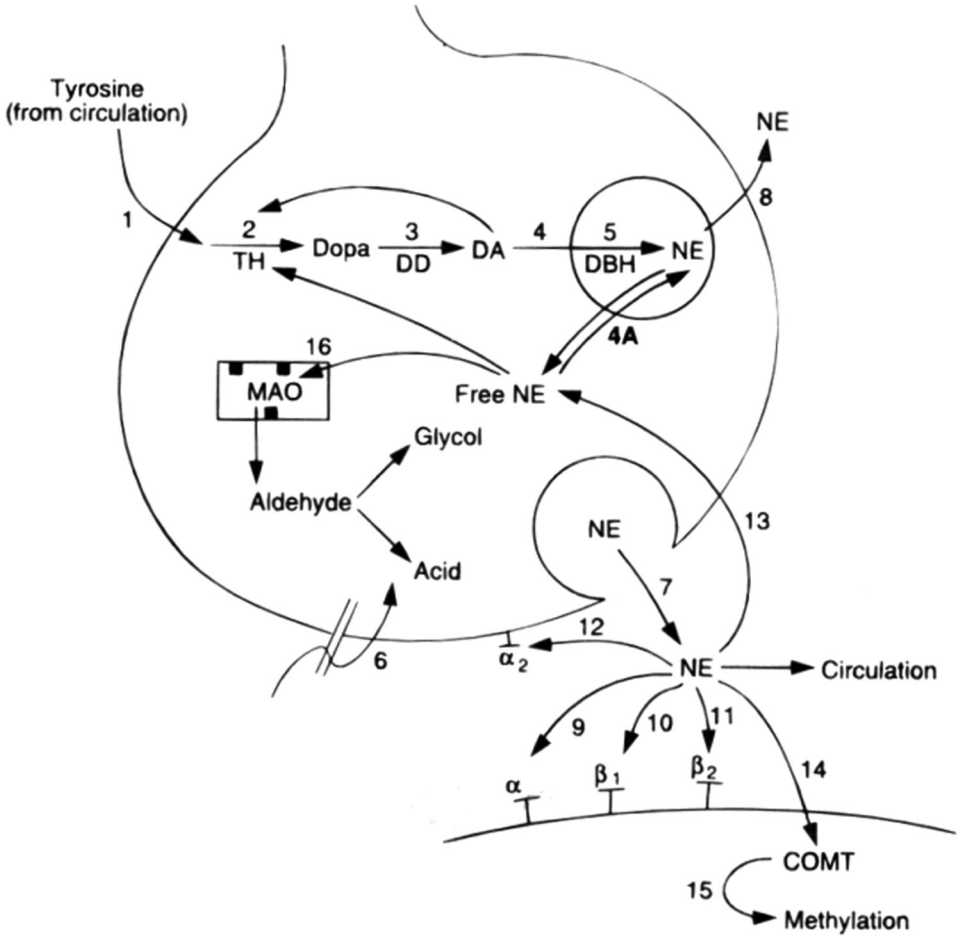


FIGURE 2-3. Site of action of drugs affecting the sympathetic nervous system. The figure depicts the events taking place at the junction of a sympathetic nerve terminal and an end-organ cell.

Tyrosine from the circulation enters the nerve terminal **(1)** and is converted first **(2)** via tyrosine hydroxylase (TH) into dopa and then **(3)** via dopa decarboxylase (DD) into dopamine (DA). DA enters the vesicle of the nerve terminal **(4)**, where it is converted **(5)**, via DA β-hydroxylase (DBH), into norepinephrine (NE), which is stored in the vesicles. Free NE in the axoplasm also enters and leaves the vesicles **(4A)**.

In the process of nerve impulse transmission across the neuroeffector junction, the nerve terminal is depolarized **(6)** by action potential. The storage vesicle fuses with the plasma membrane, and NE is released into the junction **(7)** by exocytosis. Indirect-acting sympathomimetics can also cause NE to leave the vesicles and enter the junction **(8)**.

Once released from the neuron, NE activates the postsynaptic $\alpha(\alpha_1, \alpha_2)$, β_1, and β_2 receptors **(9, 10, 11)** on the effector cell, thereby producing the response. NE also activates presynpatic α_2-receptors to inhibit further NE release **(12)**.

Several mechanisms terminate the action of NE. Most important is the reentry of NE into the nerve terminal (a process known as uptake-1) **(13)**. Some of the NE enters the effector cell (uptake-2) **(14)**, and some enters the circulation.

Two enzymes play a role in the metabolism of NE. The NE that enters the effector cell is methylated **(15)** by catechol-*O*-methyltransferase (COMT) to normetanephrine. The NE in the axoplasm of the nerve terminal is converted **(16)** by monoamine oxidase (MAO) in the neuron's mitochondria, first to the aldehyde, and then to the glycol or to vanillylmandelic acid (VMA). The glycol and the acid are the major metabolites excreted in the urine. (From Figure 2-3, *NVMS Pharmacology*.)

ii. **The liver and kidneys**, which are rich in **MAO** and **COMT**, inactivate circulating catecholamines.

(c) **Excretion.** The metabolites are excreted in the urine.

d. **Pharmacologic effects.** The pharmacologic response to an agonist is a function of the affinity of the agonist for the receptor, the number of receptors, and the efficacy of the agonist (see Table 2-1).

(1) **Epinephrine**

(a) **Blood pressure effects**

i. **Low doses** may cause little change in blood pressure. They increase skeletal muscle **blood flow** via activation of **β_2-receptors** and increase **heart rate and force of contraction via activation of β_1-receptors**. β_2-Receptors have a higher affinity than do α-receptors for Epi, producing a preferential activation at low doses.

ii. **Higher doses.** Increasing the dose of Epi leads to the activation of α-receptors, which causes **vasoconstriction** and reduces the blood flow to the skeletal musculature. **Because α-receptors predominate in the cutaneous, mesenteric, and renal vascular beds**, the net result is an increase in blood pressure.

Activation of the α-receptors increases total peripheral resistance and counters the β_2-receptor-mediated vasodilatation. In addition, the larger dose of Epi activates more β_1-receptors in the heart, which increases cardiac output and contributes to the increase in blood pressure.

As the blood pressure increases, **baroreceptors in the aorta arch and carotid sinus** are activated. They, in turn, activate the vagus nerve and **increase vagal tone** on the heart to reduce the cardiac output, lowering the systemic blood pressure.

(b) **Vascular effects**

i. **Skin.** Activation of **α-receptors causes vasoconstriction**, decreasing blood flow.

ii. **Skeletal muscle.** At low concentrations, **β_2-receptors** are activated, **increasing blood flow** to skeletal muscle. At higher concentrations, activation of α-adrenergic receptors reduces blood flow.

iii. **Mesentery and kidneys.** Activation of **α-receptors** leads to a decreased blood flow.

iv. **Lungs.** Decreased blood flow results from **vasoconstriction** of arteries and veins.

v. **Heart. Blood flow increases**, largely because of the metabolic products created by the increase in cardiac work.

(c) **Cardiac effects. β_1-Receptors** predominate in the heart, but α_1, β_2, and β_3-receptors are also present. Epi causes

i. **Increased force of contraction** (positive inotropic effect).

ii. **Increased rate of contraction** (positive chronotropic effect).

iii. **Increased output.**

iv. **Increased excitability.**

v. **Increased automaticity.**

vi. **Increased potential for** arrhythmias.

vii. **Decreased efficiency** (greater oxygen consumption).

(d) **Smooth muscle effects**

i. **Gastrointestinal (GI) tract.** Epi and NE **relax GI smooth muscle via activation of α_2- and β-receptors**, and increase the **contraction of the sphincters by activating α_1-receptors.** Activation of **α_2-receptors** in the presynaptic nerve of the parasympathetic ganglia **inhibits ACh release**, thereby decreasing parasympathetic tone.

ii. **Uterus. Contraction (mediated by α-receptors) or relaxation (mediated by β_2-receptors)** may occur, depending on the state of estrous cycle, pregnancy, and species.

iii. **Urinary bladder.** Urinary retention occurs when the fundus relaxes (as a result of β-receptor stimulation) and the trigone and sphincter contract (as a result of α_1-receptor stimulation).

iv. **Bronchioles.** Relaxation occurs via activation of β_2-receptors.
v. **Eye.** Mydriasis (pupillary dilation) results when α_1- receptors in the radial muscles of the iris are stimulated, intraocular pressure may be reduced by a local vasoconstriction that decreases the production of aqueous humor.
vi. **Spleen.** Contraction (mediated by α_1-receptors) increases blood erythrocyte levels, particularly in dogs.
vii. **Pilomotor muscles.** Contraction (mediated by α_1-receptors) erects the hairs on the skin, particularly in carnivores during fear or rage reactions.

(e) **Metabolic effects**
i. Blood concentrations of glucose, free fatty acids, and lactic acid increase when β-receptors in the liver, skeletal muscle, and adipose tissue are stimulated.
ii. Some of the effects of Epi on plasma glucose concentrations are secondary (e.g., inhibition of insulin secretion via activation of α_2-receptors and stimulation of glucagon secretion via activation of β_2-adrenergic receptors).

(2) **NE** elicits most of the effects produced by Epi that are mediated via α_1-, α_2-, and β_1-receptors, with the following exceptions:
(a) At similar doses, NE will increase the mean blood pressure more than Epi because it is not able to relax the skeletal blood vessels via β_2-adrenergic receptors.
(b) Baroreceptor activation and vagal reflex will occur at lower doses for NE than Epi. This reflex can be strong enough to decrease cardiac output despite the direct activation of cardiac β_1-receptors.

(3) DA has unique pharmacologic actions. The release of NE from the sympathetic postganglionic nerve terminal by DA contributes to its pharmacologic effects.
(a) **Activation of D_1-receptors** causes vasodilatation of the renal, mesenteric, and coronary vasculature at low rates of infusion. Natriuresis and diuresis result from the increased glomerular filtration rate and renal blood flow.
(b) **Activation of D_2-receptors in the CNS** decreases blood pressure and heart rate in the same manner as activation of α_2-adrenergic receptors in the CNS. It is unlikely that CNS D_2-receptors are activated when DA is infused, because DA does not cross the blood–brain barrier.
(c) **Activation of β_1-receptors,** which occurs at somewhat greater concentrations, produces a positive inotropic effect on the heart.
(d) **Activation of α_1-receptors** causes vasoconstriction; however, very high concentrations are necessary to produce this effect.

e. **Therapeutic uses.** Epi, NE, and DA are used parenterally or topically.
(1) **Epinephrine**
(a) Epi will reduce **bronchospasm.**
(b) Epi is used to **treat hypersensitivity** reactions and **anaphylactic shock** that is characterized by bronchospasm and hypotension.
(c) Epi reduces cutaneous blood flow, which makes it useful for **prolonging local anesthetic effects.**
(d) Applied topically, it can be used to **control localized hemorrhage**.
(e) Epi promotes the outflow of aqueous humor, making it useful for the **treatment of open-angle glaucoma.**
(f) Epi is used to **restore cardiac activity** following cardiac arrest.

(2) **NE** may be used to **correct the hypotension** induced by spinal anesthesia. It is not useful for correcting hypotension in most types of shock, because sympathetic activity is already high and further vasoconstriction may compromise the renal and mesenteric circulations.

(3) **DA** may be used to treat
(a) **Cardiogenic shock**
(b) **Septic shock**
(c) **Acute heart failure** (usually as supportive therapy)

f. Adverse effects

(1) Epinephrine

(a) Anxiety, fear, and restlessness

(b) Palpitations

(c) Cerebral hemorrhage

(d) Cardiac arrhythmias (especially in hyperthyroid patients)

(2) Norepinephrine. Adverse effects are similar to those of Epi. In addition, extravasations following IV injection may cause necrosis and sloughing at the site because of intense vasoconstriction.

(3) Dopamine. Adverse effects include those of Epi and NE, but they are short-lived because DA is rapidly metabolized.

2. Isoproterenol (Isuprel®)

a. Mechanism of action. Isoproterenol, a potent **nonselective β-receptor agonist**, increases **cyclic AMP** levels as β_1- and β_2-receptors activate adenylyl cyclase through **coupling to G_s**.

b. Pharmacologic effects

(1) IV infusion decreases mean blood pressure by reducing peripheral resistance, primarily in skeletal muscle.

(2) Cardiac output increases, owing to increases in cardiac contractility and heart rate.

(3) Smooth muscle tissues possessing β-receptors (e.g., bronchiolar and GI smooth muscle) are relaxed.

c. c. Therapeutic uses

(1) Acute bronchial constriction

(2) Complete atrioventricular (A-V) block.

d. d. Pharmacokinetics

(1) Absorption. Isoproterenol is readily absorbed parenterally or as an aerosol.

(2) Fate. It is principally metabolized by COMT and MAO, but MAO is less effective than with Epi and NE.

(3) Excretion. Metabolites are excreted in urine.

e. Adverse effects

(1) Tachycardia

(2) Arrhythmias (as a result of general stimulation of cardiac tissues).

B. Noncatecholamines

1. Phenylephrine (Neo-synephrine®)

a. Mechanism of action. Phenylephrine is an **α_1-receptor agonist** (Figure 2-4). It also has **some β-adrenergic** stimulatory properties at high doses.

b. Pharmacologic effects. Phenylephrine **increases blood pressure** (primarily by vasoconstriction).

c. Therapeutic uses. It is administered parenterally, orally, or topically.

(1) Phenylephrine has an advantage over Epi as a **vasopressor** in situations where cardiac stimulation is undesirable, such as during gas anesthesia.

(2) Phenylephrine is used as a topical nasal decongestant.

(3) It is used in ophthalmology as a **mydriatic** agent (during examinations), to reduce posterior synechiae formation, and to relieve the pain associated with uveitis.

d. Pharmacokinetics

(1) Following IV administration, vasopressor effects begin immediately and persist for $\leq$20 minutes.

(2) It is **metabolized** by the liver (to phenolic conjugates mainly after oral ingestion, and to *m*-hydroxymandelic acid after IV administration), and the effects of the drug are also terminated by uptake into tissues. The biological $t_{1/2}$ is 2–3 hours.

e. Adverse effects

(1) Phenylephrine may elicit a **reflex bradycardia** when administered IV.

(2) Hypertension, especially in geriatric, hyperthyroid, or hypertensive patients, may occur.

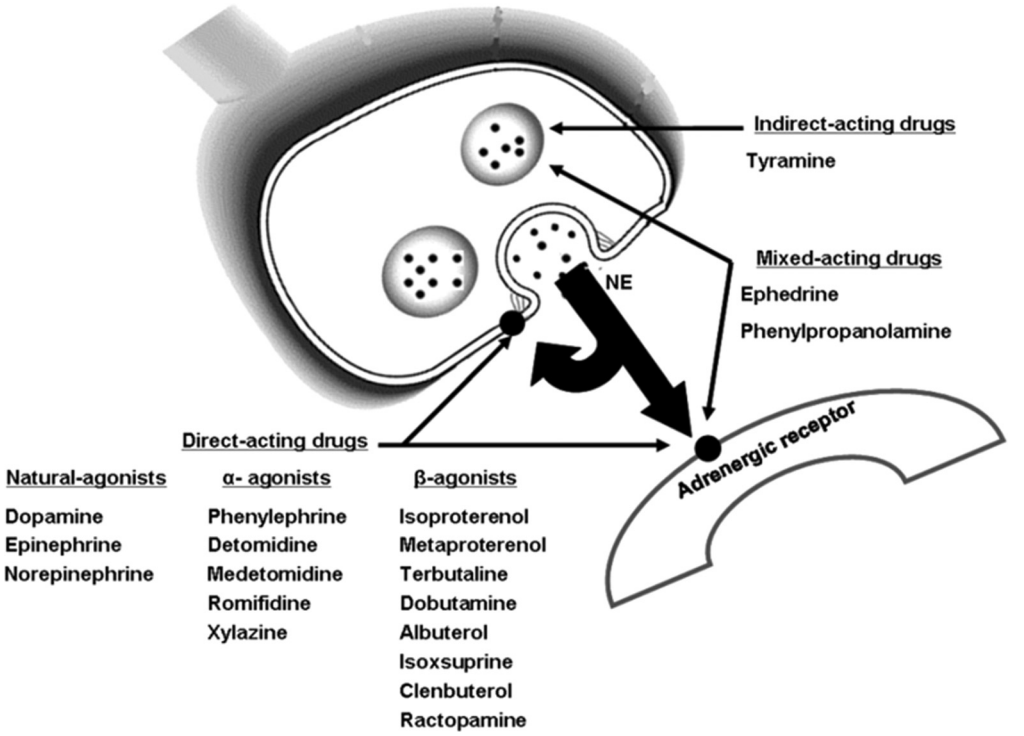


FIGURE 2-4. Comparison of direct-, mixed-, and indirect-acting sympathomimetic drugs. Direct-acting drugs are able to elicit a pharmacologic response independently of the sympathetic neuron. Indirect-acting drugs produce a response by releasing norepinephrine (NE) from the neuron after they are transported into the neuron. Mixed-acting drugs stimulate the adrenergic receptor directly and by inducing the release of NE from the neuron.

(3) **Nasal irritation** and rebound congestion may occur following long-term nasal use.

2. **Dobutamine** (Dobutrex®, see also Chapter 8)
   a. **Chemistry.** The clinically used formulation of dobutamine is the racemic mixture of two enantiomeric forms, the negative and positive isomers.
   b. **Mechanism of action.** Dobutamine activates **β_1-receptors**, and activates weakly β_2- and α_1-receptors as well.
   c. **Pharmacologic effects**
      (1) Dobutamine produces an **inotropic effect**, which is greater than its chronotropic effect.
      (2) **It increases cardiac output** by increasing cardiac contractility and stroke volume.
      (3) Increased myocardial contractility may **increase myocardial oxygen demand** and coronary blood flow.
   d. **Therapeutic uses.** Dobutamine is used for the short-term treatment of **heart failure.**
   e. **Pharmacokinetics**
      (1) Dobutamine is administered by IV infusion. Upon IV infusion, the onset of action generally occurs within 2 minutes and peaks after 10 minutes.
      (2) Dobutamine is metabolized rapidly in the liver and other tissues and has a plasma $t_{1/2}$ of 2 minutes in humans. The drug's effects diminish rapidly after cessation of therapy.
   f. **Adverse effects**
      (1) Dobutamine may increase oxygen use; therefore, it should be used with care after **myocardial infarction** to avoid increasing infarct size.
      (2) It may induce **cardiac arrhythmias**.

(3) Other adverse effects may include those described for Epi [see II A 1 f (1)].

3. **Ephedrine** (Ephedra®)
   a. **Mechanism of action.** Ephedrine is a mixed-acting agent (i.e., it has direct and indirect actions); however, its primary action is indirect. Thus, a significant portion of its action is indirectly from the **NE release. Its direct effect is activation of α_1-adrenergic receptors and β-receptors.**
   b. **Pharmacologic effects**
      (1) Ephedrine **increases blood pressure** by causing peripheral vasoconstriction and cardiac stimulation.
      (2) It causes **bronchodilation** by activating β_2-adrenergic receptors.
      (3) It causes the **urinary bladder sphincter constriction** by activating α_1-adrenergic receptors.
   c. **Therapeutic uses.** Ephedrine is a scheduled drug (i.e., additional regulations for its use are imposed by FDA).
      (1) It is used to treat **asthma-like** conditions.
      (2) It is used as a **mydriatic**.
      (3) It can be used to treat primary **urinary bladder sphincter incompetence. However, phenylpropanolamine has been used more commonly than ephedrine for urinary incontinence.**
   d. **Pharmacokinetics**
      (1) Absorption. Ephedrine is absorbed from the GI tract and can be administered orally.
      (2) Metabolism. It is resistant to metabolism by MAO and is not a substrate for COMT, so it has a prolonged action. It is metabolized very slowly in the liver and excreted mostly unchanged in the urine. Urine pH may alter excretion characteristics. In humans: at urine pH of 5, $t_{1/2}$ is ~3 hours; at urine pH of 6.3, $t_{1/2}$ is ~6 hours.
   e. **Adverse effects** are similar to those of Epi.
      (1) Hypertension and cardiac arrhythmias may occur with systemic use.
      (2) CNS stimulation may cause nervousness, nausea, and agitation.
      (3) Tachyphylaxis (i.e., diminished response following repeated administration) may occur. It is thought to be caused by a depletion of NE in the adrenergic nerve terminals susceptible to ephedrine.
4. **Phenylpropanolamine** (PPA®)
   a. **Chemistry and mechanism of action.** PPA is a mixed-acting agent (i.e., it has direct and indirect actions); however, its primary action is indirect. Thus, part of its action is indirectly from the **NE release. Its direct effect is activation of α_1-adrenergic receptors.**
   b. **Pharmacologic effects.** The effects of PPA are similar to those of ephedrine, except **PPA has little CNS stimulatory activity**.
   c. **Therapeutic uses.** PPA is used **primarily for urinary incontinence.** Tachyphylaxis has not been seen when it is used for this purpose.
   d. **Pharmacokinetics**
      (1) Absorption. PPA is absorbed from the GI tract and can be administered orally.
      (2) PPA is resistant to metabolism by MAO and is not a substrate for COMT.
      (3) The drug is partially metabolized to an active metabolite by the liver, but 80–90% is excreted unchanged in the urine within 24 hours of dosing.
      (4) The plasma $t_{1/2}$ is 3–4 hours.
   e. **Adverse effects** are similar to those of ephedrine. In addition, anorexia may occur.
5. **Terbutaline** (Brethine®) is an orally effective **β_2-receptor agonist** used as a bronchodilator. It can be administered SC as well. It is the **bronchodilator of choice for animals with heart disease, hyperthyroidism, or hypertension**; however, it should be administered with caution because **high doses may stimulate β_1-receptors**. Terbutaline can be administered parenterally or orally.
   a. **Pharmacokinetics**
      (1) No information is available for dogs and cats. Terbutaline has **a high p*K*a (10.1)**; as a result, **most of terbutaline is in ionized form at physiological**

pH. In humans, <50% of oral dose is absorbed because of the high p*K*a value for this drug; peak bronchodilation occurs within 3 hours and lasts for ≤8 hours. It is well absorbed following SC administration, peak bronchodilation occur within 1 hour, and lasts for ≤4 hours.

(2) **In horses, terbutaline should not be administered orally, since <1% is being absorbed via this route.** When administered IV, bronchodilation lasts for ~30 minutes. Thus, terbutaline should be administered as constant infusion when given IV.

(3) Terbutaline is excreted mainly as the parent drug in the urine (60%), the rest as metabolites (sulfate conjugate).

b. **Adverse effects.** Tachycardia, tremors, and excitation may be seen, particularly at high doses. Sweating may be seen in horses.

6. **Albuterol** (Torpex®)

a. **Mechanism of action.** Albuterol is a selective **β_2- agonist**, which causes bronchodilation.

b. **Therapeutic uses.** Albuterol is used as an aerosol and oral tablets, mainly in dogs, cats, and horses as a bronchodilator and for its effects on bronchial smooth muscle to alleviate bronchospasm or cough.

c. **Pharmacokinetics**

(1) **Albuterol has a high p*K*a (9.3)**, thus most of the compound is in ionized form in the blood and other tissues at physiological pH. The absorption following oral administration is limited because of the high p*K*a value for this drug. The absorption following inhalation is rapid and complete; bronchodilation occurs within 5 minutes of inhalation.

(2) **Duration of bronchodilation** generally persists for 1–7 hours after inhalation and ≤12 hours after oral administration.

(3) **Albuterol is extensively metabolized** in the liver, principally to the inactive metabolite, albuterol 4′ – *O*-sulfate, which is excreted into urine. Plasma $t_{1/2}$ is 3–5 hours after oral administration.

7. **Isoxsuprine** (Vasodilan®)

a. **Pharmacologic effects and mechanism of action. Isoxsuprine is a selective β_2-adrenergic agonist**, which causes vasodilatation in skeletal muscle. In horses with navicular disease, isoxsuprine raises distal limb temperatures. Isoxsuprine also relaxes uterine smooth muscle and may increase heart rate and contractility. At high doses, isoxsuprine can decrease blood viscosity and reduce platelet aggregation.

b. **Therapeutic uses. Isoxsuprine is used to treat navicular disease in horses**, and should be administered IV; the efficacy is disappointing when used orally.

c. **Pharmacokinetics.** Very limited information is available for horses. After oral administration of isoxsuprine, the plasma concentrations of the drug are highly variable. The elimination $t_{1/2}$ is ~3 hours in horses.

d. **Adverse effects.** Horses may show signs of **CNS stimulation** (uneasiness, hyperexcitability, nose-rubbing) or **sweating, hypotension, and tachycardia**.

8. **Clenbuterol** (Ventipulmin® Syrup)

a. **Mechanism of action.** Clenbuterol is a selective **β_2-adrenergic agonist**.

b. **Therapeutic uses.** Clenbuterol is used in horses as a **bronchodilator** for airway obstruction, such as chronic obstructive pulmonary disease. It had been **misused as a repartitioning agent** before ractopamine became available. It is administered orally.

c. **Pharmacokinetics**

(1) After oral administration to horses, plasma levels of clenbuterol peak at 2 hours and $t_{1/2}$ is ~12 hours.

(2) Urinary concentrations of clenbuterol are 100 times of those found in the plasma and can persist for 12 days in urine after the last oral dosing.

d. **Adverse effects**

(1) Muscle tremors, sweating, restlessness, urticaria, and tachycardia may be noted, particularly early in the course of therapy. Increase in serum creatine kinase concentrations (an indicator for muscle damage) has been noted in some horses and ataxia can occur.

(2) Clenbuterol can induce tachycardia at high doses. Thus, it **should not be used in horses suspected of having cardiovascular impairment.**
(3) Clenbuterol can induce **uterine relaxation**, which may offset the effects of oxytocics, for example, oxytocin and prostaglandin $F_{2\alpha}$.

9. **Ractopamine** (Optaflexx®, Paylean®). This is **one of the two approved repartitioning agents for animals.** It is used in cattle and swine.
   a. **Mechanism of action.** Ractopamine is a selective **β_2-adrenergic agonist.**
   b. **Therapeutic uses.** Ractopamine is used as a feed additive to improved rate of weight gain, feed efficiency, and increase carcass Leanness. Ractopamine increases lipolysis.
   c. **Pharmacokinetics**
      (1) The **p*Ka*** of ractopamine is **9.4**, thus it is mostly **in ionized form when present in the blood or tissues at the physiological pH of 7.4.** As a result, the **GI absorption of ractopamine is low**, and the tissue concentrations of the drug are also low following oral administration. **No preslaughter withdrawal period is needed when animals are on ractopamine.**
      (2) Ractopamine is metabolized in the liver into glucuronide form, and the latter is excreted mostly into urine. Thus, both liver and kidney have the highest levels of residues. The residues in liver and kidney decline rapidly, that is, after a 24-hour withdrawal period, only 45% and 10% of the total residues present after a zero-day withdrawal period remained in liver and kidney, respectively.
   d. **Adverse effects.** Anorexia, bloat, and locomotion disorder have been seen. Personnel protection is needed when handling ractopamine. **Persons with cardiovascular disease should exercise special caution to avoid exposure.**
10. **Zilpaterol (Zilmax®).** It is a new and selective β_2-agonist that is used as a repartitioning agent in beef cattle. The pharmacokinetics of zilpaterol are largely unknown. The preslaughter withdrawal period is 48 hours.

III. ADRENERGIC ANTAGONISTS

A. α-Adrenergic antagonists

1. **Phenoxybenzamine** (Dibenzyline®)
   a. **Mechanism of action.** Phenoxybenzamine differs from most α_1-receptor antagonists in that it **binds covalently to the α_1-receptor.** This is a stable chemical bond that **produces a long-lasting and irreversible block of the receptor.**
   b. **Pharmacologic effects**
      (1) Phenoxybenzamine **decreases total peripheral resistance,** causing hypotension.
      (2) **Heart rate may be increased** via de-activation of the baroreceptor reflex.
      (3) **Phenoxybenzamine can block pupillary dilation,** lid retraction, and contraction of the nictitating membrane.
   c. **Therapeutic uses. It is administered orally.**
      (1) In dogs and cats, phenoxybenzamine **reduces hypertonus at the urethral sphincter.**
      (2) In horses, phenoxybenzamine has been used to **treat laminitis and secretory diarrhea**.
   d. **Pharmacokinetics.** No information is available for animals. In humans, it is poorly absorbed from the GI tract with a bioavailability of 20–30%. Onset of action of the drug is slow (several hours) and increases over several days after regular dosing. Effects persist for 3–4 days after discontinuation of the drug.

      Phenoxybenzamine is highly lipid soluble and may store in adipose tissue. It is metabolized (dealkylated) and excreted in both the urine and bile. The plasma $t_{1/2}$ is ~24 hours in humans.

e. **Adverse effects**
   (1) **Hypotension** may be enhanced in hypovolemic animals.
   (2) **It should not be used in horses with colic**.

2. **Prazosin** (Minipress®)
   a. **Mechanism of action.** Prazosin is a competitive and selective α_1**-receptor antagonist**.
   b. **Pharmacologic effects**
      (1) **Prazosin relaxes arterial and venous smooth muscle.**
      (2) There is a decrease in total peripheral resistance. High doses may cause **hypotension.**
   c. **Therapeutic uses. It is administered orally.**
      (1) Prazosin is used in the treatment of **congestive heart failure**. It decreases arterial pressure, which **improves cardiac output.**
      (2) Prazosin is also used in the treatment of **hypertension**.
   d. **Pharmacokinetics.** No information is available for animals. In humans, it is variably absorbed after oral administration. Peak levels occur in 2–3 hours. It is widely distributed throughout the body and is ~97% bound to plasma proteins. It is metabolized in the liver and some metabolites are active. Metabolites and ≤10% of unchanged drug are eliminated in feces.
   e. **Adverse effects include diarrhea, tachycardia, hypotension, and fluid retention.**

3. **Phentolamine** (Regitine®)
   a. **Mechanism of action.** Phentolamine is a **competitive** α_1**- and** α_2**-receptor antagonist**.
   b. **Pharmacologic effects**
      (1) Heart rate may be increased by de-activation of the baroreceptor reflex or by blocking the presynaptic α_2-receptors of the heart.
      (2) Blood pressure is lowered by inhibition of α_1- and α_2-receptors in vascular smooth muscle.
   c. **Therapeutic uses.** Phentolamine is administered IV or IM to treat hypertension and to **control high blood pressure resulting from sympathomimetic amine overdose.**
   d. **Pharmacokinetics.** No information is available for animals. In humans, it is metabolized in the liver and is excreted into the urine mostly as metabolites. The elimination $t_{1/2}$ is ~20 minutes.
   e. **Adverse effects.** Tachycardia is frequently observed.

4. **Yohimbine** (Yobin®, see also Chapter 4).
   a. **Mechanism of action.** Yohimbine is a competitive α_2**-receptor antagonist** that promotes the formation of cyclic AMP by blocking α_2-receptor activation.
   b. **Pharmacologic effects**
      (1) **Yohimbine can cause CNS stimulation, increased heart rate, and increased blood pressure by increasing NE release from the adrenergic nerve endings.**
      (2) **Yohimbine can increase GI motility by increasing parasympathetic tone.**
      (3) Yohimbine may increase plasma insulin levels, because α_2-receptors inhibit insulin release.
   c. **Therapeutic uses.** Yohimbine is used IV and IM in **monogastric animals to reverse the effects of** α_2**-receptor agonists** (i.e., xylazine, detomidine, medetomidine, and romifedine) and amitraz, a miticide that has α_2-agonistic activities. Yohimbine is marginally effective in ruminants.
   d. **Pharmacokinetics**
      (1) Yohimbine is distributed evenly after IV administration. The total body clearance is 35 mL/min/kg in horses and 30 mL/min/kg in dogs.
      (2) The $t_{1/2}$ of the drug is 0.5–1.5 hours in horses and 1.5–2 hours in dogs.
   e. **Adverse effects** are primarily **CNS stimulation, tachycardia, hypertension, and increase in GI motility.**

5. **Tolazoline.** It is a competitive antagonist for α_1- and α_2-receptors. The pharmacologic effects are similar to phentolamine.

a. Therapeutic uses. It is administered IV (slowly) to reverse the pharmacologic effects of α_2-agonists, for example, xylazine, **particularly in ruminants.**

b. Pharmcokinetics. After IV administration in horses, it is widely distributed. It is concentrated in the liver and kidneys. The plasma $t_{1/2}$ in horses is ~60 minutes. In cattle after an IV dose of 4 mg/kg, the concentration of tolazoline was <10 μg/kg by 96 hours in tissues and by 48 hours in milk. On the basis of these data, it is recommended the preslaughter withdrawal period of 8 days and milk withdrawal time of 48 hours in cattle.

c. Adverse effects. Tolazoline can cause tachycardia, hypotension, and increased GI motility. Because of hypotension, it should not be administered to animals exhibiting signs of stress, debilitation, cardiac disease, sympathetic blockage, hypovolemia, or shock.

6. Atipamezole. It is an α_2-antagonist, which is labeled for use as a reversal agent for medetomidine. It can reverse the effects of other α_2-agonists as well (e.g., amitraz, xylazine). It is effective in all species, including ruminants. However, it is too expensive to be used in food animals.

a. Pharmacokinetics. It is administered IM, IV, or SC, but IM route is preferred. After IM administration in the dog, peak plasma levels occur in 10 minutes. It is metabolized in the liver to compounds that are eliminated in the urine. The elimination $t_{1/2}$ is 2–3 hours.

B. β-Adrenergic antagonists

1. Propranolol (Inderal®, see also Chapter 8).

a. Mechanism of action. Propranolol is a **nonselective β-receptor antagonist** that competitively blocks both β_1- and β_2-receptors. Recent evidence indicates propranolol is an inverse agonist of β-receptors.

b. Pharmacologic effects

(1) Propranolol decreases the sinus heart rate and depresses A-V conduction.
(2) It decreases cardiac output.
(3) It decreases myocardial oxygen demand.
(4) It decreases the automaticity of cardiac tissue.
(5) It increases airway resistance.

c. Therapeutic uses. It is administered IV, IM, SC, or orally for following conditions:

(1) Propranolol is used to treat **cardiac arrhythmia and hypertension associated with thyrotoxicosis and pheochromocytoma**, respectively.
(2) It is used to treat **arrhythmias** (e.g., atrial and ventricular premature complexes and supraventricular and ventricular tachycardia).

d. Pharmacokinetics

(1) Absorption. Propranolol is well absorbed following oral administration.
(2) Propranolol is highly lipid soluble and readily crosses the blood–brain barrier.
(3) The $t_{1/2}$ in dogs is 1–2 hours and <2 hours in horses.
(4) There is a significant first-pass effect, which reduces the systemic bioavailability. In dogs, only 2–27% of an oral dose reaches the blood. Rapid metabolism occurs in the liver to form 4-hydroxypropranolol, which is followed by conjugation. More than 99% of propranolol is excreted as metabolites.

e. Adverse effects

(1) Up-regulation of β-receptors (i.e., an increased number of receptors) occurs with long-term therapy.
(2) Abrupt cessation of therapy may lead to excessive stimulation of β-receptors, thereby exacerbating the symptoms.

f. Contraindications

(1) Propranolol may cause **bronchospasm** and is contraindicated in asthmatic animals.

(2) Propranolol is contraindicated in animals with **heart failure or sinus bradycardia**.
(3) It is contraindicated in animals with **hepatic disease.**

2. **Atenolol** (Tenormin®)
   a. **Mechanism of action.** Atenolol is a competitive **β_1-receptor antagonist.**
   b. **Pharmacologic effects.** Atenolol decreases heart rate, cardiac output, and systolic and diastolic pressures.
   c. **Therapeutic uses.** Atenolol is administered orally to treat **supraventricular arrhythmias, hypertrophic cardiomyopathy** in cats, and hypertension.
   d. **Pharmacokinetics**
      (1) Atenolol has low lipid solubility and unlike propranolol, only small amounts of atenolol are distributed into the CNS.
      (2) Atenolol is minimally biotransformed in the liver; 40–50% is excreted unchanged in the urine and the bulk of the remainder is excreted in feces as the parent compound.
      (3) The plasma $t_{1/2}$ in dogs is 3.2 hours and in cats, it is 3.7 hours. Duration of β-adrenergic blockade in cats is ~12 hours.
   e. **Adverse effects**
      (1) Although atenolol is selective for β_1-receptors, it should be used cautiously in animals with asthma or a history of bronchospasm, because at high doses it can block β_2-receptors as well.
      (2) Excessive β_1-blockade can greatly reduce cardiac output.
      (3) It is a negative inotrope, so it must be used with caution in patients with congestive heart failure, in renal failure patients, and in patients with sinus node dysfunction.
      (4) Atenolol can cause lethargy, hypotension, or diarrhea.

3. **Metoprolol** (Lopressor®)
   a. **Mechanism of action.** Metoprolol is a selective **β_1-receptor antagonist**. However, at high doses it blocks β_2-receptors as well.
   b. **Pharmacologic effects**
      (1) Cardiovascular effects secondary to metoprolol's negative inotropic and chronotropic actions include decreased sinus heart rate, slowed AV conduction, diminished cardiac output, decreased myocardial oxygen demand, reduced blood pressure, and inhibition of the β-agonist-induced tachycardia.
      (2) Metoprolol does not possess membrane-stabilizing activity like propranolol.
   c. **Therapeutic uses.** Metoprolol can be used to treat **supraventricular tachyarrhythmias**, **premature ventricular contractions, systemic hypertension, hypertrophic cardiomyopathy, and thyrotoxicosis** in cats. It is administered orally at every 12 hours. Because metoprolol is relatively safe to use in animals with bronchospastic disease, it is often chosen over propranolol.
   d. **Pharmacokinetics**
      (1) Metoprolol tartrate/succinate is rapidly and nearly completely absorbed from the GI tract, but it has a relatively high first-pass effect (50%) so systemic bioavailability is reduced.
      (2) Metoprolol has very low protein binding characteristics (5–15%) and is distributed well into most tissues.
      (3) Metoprolol crosses the blood–brain barrier, and CSF levels are ~80% of those found in the plasma.
      (4) Metoprolol is metabolized in the liver; unchanged drug and metabolites are then principally excreted in the urine. The reported $t_{1/2}$ in dogs is 1.6 hours and in cats it is 1.3 hours.
   e. **Adverse effects.** They are similar to the adverse effects of propranolol.

4. **Esmolol** (Brevibloc®)
   a. **Mechanism of action.** Esmolol is a selective **β_1-receptor antagonist. Not like propranolol, it has little membrane-stabilizing activity.**
   b. **Therapeutic uses. Esmolol and propranolol are the first choices for IV use for tachyarrhythmias** and occasionally for acute management of dynamic left

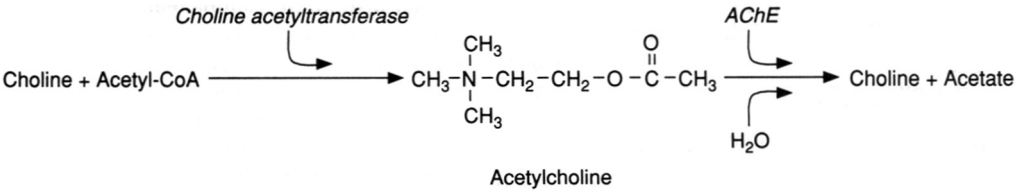


FIGURE 2-5. Synthesis and hydrolysis of acetylcholine (ACh). CoA, coenzyme A; AChE, acetylcholinesterase.

ventricular outflow obstruction in cats. **Esmolol, very short-acting (~20 minutes), is still used in selected cases and can "test" whether a β-adrenergic antagonist would be helpful, while not lasting long if it is not.**

c. **Pharmacokinetics.** Esmolol has a plasma $t_{1/2}$ of ~10 minutes. The short duration of action of esmolol is attributable to **rapid enzymatic hydrolysis by red blood cell esterases**.

d. **Adverse effects.** Excessive β_1-blockade can greatly reduce cardiac output.

2. **Sotalol** (Betapace®)

a. **Mechanism of action.** Sotalol is **a nonselective β-receptor antagonist**, which can selectively prolong the duration of action potential and refractory period (see Chapter 8).

b. **Therapeutic uses.** Sotalol is **a class III antiarrhythmic drug,** which can be used orally to treat **ventricular tachycardias** in dogs.

c. **Pharmacokinetics.** Unlike propranolol, **sotalol does not have any appreciable first-pass effect after oral administration**. Food may reduce the bioavailability of sotalol by 20% (human data). The drug has relatively low lipid solubility and virtually no protein binding. Elimination is almost all via the kidney and most of the drug is excreted unchanged. In dogs, sotalol's elimination $t_{1/2}$ is 5 hours.

d. **Adverse effects.** At high doses, sotalol may show negative inotropic effects and proarrhythmic effects. Sotalol may cause dyspnea/bronchospasm, fatigue/dizziness, and nausea/vomiting.

IV. CHOLINERGIC AGONISTS (Table 2-2)

A. Acetylcholine (ACh)

1. **Chemistry and biosynthesis (Figure 2-5).** ACh is a quaternary chemical, synthesized by the enzyme choline acetyltransferase from choline and acetyl coenzyme A (acetyl-CoA).
2. **Mechanism of action.** ACh stimulates muscarinic and nicotinic receptors.
3. **Pharmacologic effects (see Tables 2-1 and 2-2)**

a. **Cardiovascular.** The actions of ACh on the heart are similar to the effects produced by vagal stimulation. ACh decreases systemic blood pressure following IV injection. Possible mechanisms include negative inotropic or chronotropic action and vasodilatation.

(1) **Vasodilatation** in response to nerve-released ACh is of little physiologic importance in the maintenance of blood pressure, because most peripheral blood vessels are not cholinergically innervated. However, drugs that are analogs of ACh are capable of producing vasodilatation via activation of muscarinic receptors in the blood vessels.

(2) **Vasodilatation** is thought to be caused by two processes as follows:

(a) **Inhibition of the release of NE from the sympathetic nerve terminal by activating M_2-receptors.**

(b) **Interaction with M_3-receptors on the endothelial cells to release nitric oxide, which initiates the relaxation of vascular smooth muscle.**

b. Smooth muscle and glands

(1) Stimulation of muscarinic M_3-receptors increases GI motility and secretion.

(2) ACh causes smooth muscle contraction in the uterus, ureters, bladder, bronchi, and sphincter muscles of the iris via activation of M_3-receptors.

(3) Activation of M_3-receptors increases salivary and lacrimal gland secretions.

4. **Therapeutic uses.** ACh has little or no use as a therapeutic drug, but it is used topically to **constrict pupil** in intraocular surgery.
5. **Antagonists. Atropine** is a specific antagonist at muscarinic receptors.

B. Carbachol (Carbamylcholine, Carbastat®, etc.)

1. **Chemistry.** Carbachol has a carbamic acid-ester bond that is not hydrolyzable by cholinesterase. Like ACh, carbachol is a quaternary nitrogen compound.
2. **Mechanism of action.** Carbachol activates both muscarinic and nicotinic receptors.
3. **Therapeutic use.** Carbachol is used topically to produce **miosis** in ophthalmology. It could be administered SC to treat GI and uterine atony, but its use in such cases should be performed with extreme caution to prevent rupture of the tracts.
4. **Pharmacokinetics.** No information is available for animals.

C. Bethanechol

1. **Chemistry.** Bethanechol chemically resembles carbachol and is a **quaternary** compound. It is resistant to hydrolysis by cholinesterase.
2. **Pharmacologic effect.** Bethanechol is an **agonist of muscarinic receptors**.
3. **Therapeutic uses.** Bethanechol is administered SC to treat the **distention of the urinary bladder** by increasing contractility. It could be administered SC to treat **GI and uterine atony**, but its use in such cases should be performed with extreme caution to prevent rupture of the tracts.
4. **Pharmacokinetics.** No information is available for animals. Because bethanechol is a quaternary ammonium compound, the **GI absorption is nil** after oral administration.

D. Pilocarpine

1. **Chemistry.** Pilocarpine is a **tertiary amine** alkaloid.
2. **Pharmacologic effects.** Pilocarpine resembles carbachol in actions; however, because it does not contain a quaternary ammonium, it can cross the biologic membranes.
3. **Therapeutic uses.** Pilocarpine is primarily used topically to produce **miosis** and to lower **intraocular pressure** in glaucoma.
4. **Pharmacokinetics.** No information is available for animals.
5. **Adverse effects**

(1) Pilocarpine can cause local irritation and inflammation of the uveal tract.

(2) With repeated use, pilocarpine may cause systemic effects (**vomiting, diarrhea, and increased salivation**).

V. ANTICHOLINESTERASE AGENTS (INDIRECT CHOLINERGIC AGONISTS)

A. Mechanism of action. These agents act indirectly by **preventing the hydrolysis of ACh by acetylcholinesterase** (AChE). Therefore, at synaptic junctions, more cholinergic receptors are occupied by ACh, causing increased muscarinic and nicotinic responses. Anticholinesterase (anti-ChE) agents prevent the hydrolysis of ACh via three following **primary mechanisms**:

1. **Reversible AChE inhibition.** The quaternary nitrogen of the drug reversibly binds to the active center of the enzyme at the anionic site.
2. **Carbamylation of AChE.** The carbamates are substrates for AChE and occupy the active site for an extended period of time, thereby increasing the ACh concentration at synapses.
3. **Phosphorylation of AChE.** The organophosphates form a stable covalent bond with the enzyme, and their effects are long-lasting (Figure 2-5).

B. Preparations

1. **Carbamates**
   - **a. Physostigmine** (Antilirium®)
     - **(1) Chemistry.** Physostigmine is a tertiary amine.
     - **(2) Pharmacologic effects.** The pharmacologic effects mimic those of ACh.
       - **(a)** Physostigmine produces miosis, salivation, and increased GI motility.
       - **(b)** In large doses, it causes fasciculation followed by paralysis of skeletal muscle (caused by the accumulation of ACh at the neuromuscular junction).
     - **(3) Therapeutic uses.** Physostigmine can be used topically to treat simple and secondary **glaucoma**, and can be used IM, SC, or orally to counteract intoxication by atropine and other antimuscarinic drugs.
     - **(4) Pharmacokinetics.** Physostigmine is well absorbed from the GI tract, SC tissues, and mucous membranes. It crosses the blood–brain barrier. It is largely hydrolyzed at the ester linkage by plasma esterases. Duration of action is 3–6 hours.
   - **b. Neostigmine** (Prostigmin®)
     - **(1) Chemistry.** Neostigmine contains a quaternary ammonium.
     - **(2) Pharmacologic effects**
       - **(a)** The pharmacologic effects of neostigmine mimic those of ACh, causing effects similar to those of physostigmine.
       - **(b)** Neostigmine reverses the neuromuscular block produced by tubocurarine-like drugs by
         - **i.** Inhibition of AChE
         - **ii.** Increasing the release of ACh from nerve endings
         - **iii.** Acting directly on the skeletal neuromuscular junction
     - **(3) Therapeutic uses.** It is administered SC, IM, or IV to treat the following conditions:
       - **(a)** Reversal of tubocurarine-like blockade at the skeletal neuromuscular junction
       - **(b)** Paralytic ileus
       - **(c)** Atony of the urinary bladder
       - **(d)** Myasthenia gravis-like conditions
     - **(4) Pharmacokinetics**
       - **(a) Absorption.** Typical of quaternary ammoniums, neostigmine is not well absorbed orally nor does it cross the blood–brain barrier.
       - **(b) Metabolism.** Neostigmine is hydrolyzed by plasma esterases.
       - **(c) Excretion.** It is excreted in the urine as parent compound. Duration of action is 0.5–2 hours.
     - **(5) Adverse effects and contraindications.** Adverse effects of neostigmine are **cholinergic** in nature. It is contraindicated in the presence of **GI or urinary obstruction**.
   - **c. Edrophonium** (Tensilon®, etc.)
     - **(1) Pharmacologic effects.** Like neostigmine, edrophonium is a quaternary ammonium compound. Its actions are similar to those of neostigmine.
     - **(2) Therapeutic uses.** Edrophonium is used to diagnose myasthenia gravis-like disease and antagonize tubocurarine-like drugs.
     - **(3) Pharmacokinetics.** Edrophonium is administered parenterally and has a short duration of action (10–15 minutes). Other aspects of pharmacokinetics have not been well-described.

(4) **Adverse effects** are generally dose-related and cholinergic in nature. Severe adverse effects are possible with large overdoses.

d. Pyridostigmine (Mestinon®) and **demecarium** are similar to neostigmine (quaternary compounds); however, they have a longer duration of action of 4–6 hours. Pyridostigmine is used orally to treat myasthenia gravis, but should be given parenterally to increase effectiveness of the treatment. Demecarium is used topically to treat glaucoma. Adverse effects are similar to those of neostigmine.

e. Carbaryl and propoxur are carbamate ectoparasiticides. See Chapter 16 for further information. The effects of overdose are similar to organophosphate poisoning and are treatable with atropine.

2. Organophosphates

a. Preparations

(1) Echothiophate. It is a quaternary organophosphate (OP), and has a long duration of action (>12 hours). It is used topically in the treatment of open angle glaucoma.

(2) OPs used as ectoparasiticides are discussed in Chapter 16.

b. Adverse effect (see also Chapter 16)

(1) Clinical signs

(a) SLUDD (i.e., salivation, lacrimation, urination, defecation, and dyspnea) refers to a constellation of signs that are related to muscarinic stimulation. In addition, miosis and bradycardia may be seen.

(b) Anorexia and vomiting may occur.

(c) Neurologic signs include convulsions and fasciculation of skeletal muscle. Respiratory failure caused by inhibition of respiratory center, bronchial spasm and excessive secretions, and weakness of the respiratory muscles ultimately leads to death.

(2) Treatment

(a) Detoxification

i. Dermal exposure. The skin should be washed with soap and water to remove unabsorbed toxin. These chemicals are highly lipid-soluble and are readily absorbed via the skin; therefore, personnel should wear protective gear to prevent contact with the toxin.

ii. Oral exposure. Gastric lavage should be considered if the organophosphates have been ingested.

(b) Stabilization

i. Respiratory assistance may be required.

ii. Anticonvulsants may be administered.

(c) Antidotal therapy

i. Atropine will reduce the muscarinic effects.

ii. Pyridine-2-aldoxime methiodide (2-PAM, pralidoxime) reactivates AChE (Figure 2-6).

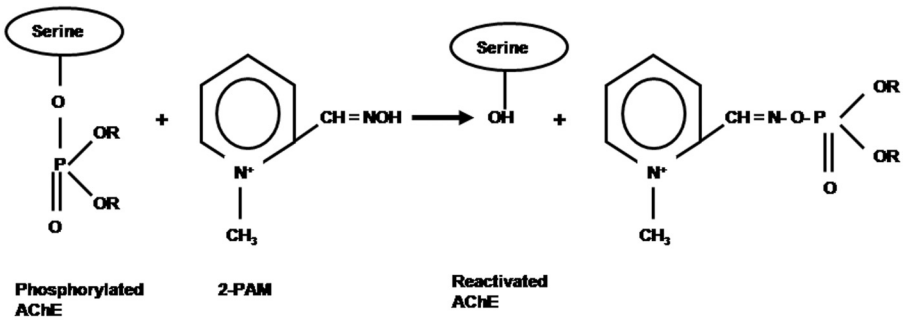


FIGURE 2-6. Pralidoxime (2-PAM) reactivates acetylcholinesterase (AChE). An organophosphate phosphorylates AChE by binding to the serine residue of the enzyme. 2-PAM works by binding to the organophosphate, which then pulls the compound from ACh, regenerating the enzyme.

VI. PARASYMPATHETIC ANTAGONISTS (ANTIMUSCARINIC DRUGS)

A. Atropine sulfate

1. **Chemistry.** Atropine, a tertiary amine, is the prototype for all antimuscarinic drugs. It is an alkaloid obtained from the plant *Atropa belladonna* (deadly nightshade).
2. **Mechanism of action. Atropine is a competitive and nonselective antagonist of ACh at muscarinic receptors.**
3. **Pharmacologic effects**
   a. **Heart**
      (1) **Heart rate.** The effect of atropine on the heart rate is variable.
         (a) The rate may be slow initially or following a low dose, possibly as a result of central vagal stimulation.
         (b) As the muscarinic receptors on the sinoatrial (SA) node are blocked by higher concentrations of atropine, tachycardia results.
      (2) The PR interval is shortened.
   b. **Vasculature.** Because blood vessels are regulated primarily by the sympathetic nervous system, atropine at therapeutic doses has a small to modest effect on the systemic blood pressure.
   c. **CNS.** Toxic doses of atropine produce excitation, possibly followed by depression as the toxicity progresses.
   d. **Smooth muscle**
      (1) **GI contractions are reduced in amplitude and frequency.** Muscle tone is also reduced.
      (2) Biliary tract smooth muscle is relaxed.
      (3) **Urinary bladder and ureter tone is reduced.**
      (4) **Bronchodilation** occurs in the large bronchi.
   e. **Eye**
      (1) **Mydriasis.** Atropine blocks the muscarinic receptors for ACh on the sphincter smooth muscle of the iris.
      (2) **Cycloplegia** is the inability to accommodate for near vision. Atropine inhibits cholinergic control of the ciliary muscle of the lens.
      (3) Sweat gland secretions are reduced.
      (4) Gastric secretions are reduced at high doses.
4. **Therapeutic uses.** It is administered IV, IM, SC, or orally.
   a. **Atropine** is used as a **preanesthetic agent to reduce salivary and respiratory Secretions.**
   b. Antimuscarinic agents are used in ophthalmology to produce **cycloplegia and mydriasis**; however, because atropine has a **long duration of action**, its usefulness in this capacity is limited.
   c. It may be used to treat **renal and biliary colic** when combined with opioids.
   d. **It is used to counter anti-ChE overdose or toxicity.**
   e. It may be useful in treating mushroom toxicity if **muscarine** is the toxic agent.
5. **Pharmacokinetics**
   a. Atropine is rapidly and well absorbed when given orally or parenterally. After IV administration, peak effects in heart rates occur within 3 minutes.
   b. Atropine is well distributed throughout the body and crosses into the CNS.
   c. Atropine is metabolized into noratropine, atropin-*n*-oxide, and tropic acid by the liver and excreted into the urine. Thirty to fifty percent of a dose is excreted unchanged into the urine. The $t_{1/2}$ of atropine is ~2.5 hours, and most of the drug is excreted in the urine within the first 12 hours.
6. **Adverse effects include tachycardia, photophobia (from mydriasis), xerostomia, increased body temperature in horses (caused by a decrease in sweating), restlessness, disorientation, and CNS stimulation.**
7. **Treatment of toxicity.** An anti-ChE agent (e.g., neostigmine, physostigmine) should be administered to increase the concentration of ACh at muscarinic receptor sites. **CNS stimulation may be controlled by benzodiazepines.**

B. **Scopolamine (hyoscine) and *N*-butylscopolammonium (Bucospan®), alkaloids resemble atropine** in chemical structure and pharmacologic properties. Scopolamine can be used orally to control motion sickness. *N*-butylscopolammonium is administered IV in horses as an antispasmodic and antimuscarinic drug to treat colic and intestinal impaction. These two drugs may produce excitement or sedation.

C. **Propantheline** (Pro-Banthine®)

1. **Chemistry.** Propantheline is a synthetic quaternary ammonium antimuscarinic agent.
2. **Therapeutic uses**
   a. In small animals, propantheline is used orally as an **antispasmodic/antisecretory** agent in the treatment of diarrhea, colitis, and acute irritable bowel syndrome. It is also used orally in the treatment of hyperreflexic detrusor or urge **urinary incontinence** and as oral treatment in anticholinergic responsive **bradycardias**. However, doubts have been raised with the effectiveness, since GI absorption of the drug is rather poor.
   b. In horses, propantheline has been administered IV to reduce **colonic peristalsis** and to relax the rectum to allow easier **rectal examination and perform surgical procedures** to the rectum.
3. **Pharmacokinetics.** It is poorly absorbed after oral administration, only <25% of oral dose is absorbed. After being absorbed, it cannot penetrate the blood–brain barrier. After oral administration, it is believed to be prevalently metabolized (hydrolyzed) in the GI and/or liver; <5% of an oral dose is excreted unchanged in the urine. The plasma $t_{1/2}$ in humans is 1.6 hours and duration of action is 6 hours; no information is available for animals.
4. **Adverse effects** are similar to those of atropine, except propantheline does not effectively enter the CNS, since it is a quaternary ammonium compound.

D. **Glycopyrrolate** (Robinul®-V)

1. **Chemistry.** Glycopyrrolate is a synthetic quaternary ammonium.
2. **Therapeutic uses**
   a. It is used as a preanesthetic drug by parenteral administration (IV, IM, or SC).
   b. It can be administered IV or IM to treat sinus bradycardia, S-A arrest, and incomplete A-V block.
   c. It can be administered SC to control hyersalivation in cats.
3. **Pharmacokinetics**
   a. After parenteral administration, it does not effectively enter the CNS or eye.
   b. After IM administration, plasma levels reach at peak in 30–45 minutes. Vagal blocking actions persist for 2–3 hours and antisalivation effect persists up to 7 hours.
   c. It is eliminated primarily via the kidney; metabolism plays a small role in its elimination. The plasma $t_{1/2}$ is ~1 hour after IM or IV administration..

E. **Tropicamide**, a synthetic tertiary amine antimuscarinic drug, is used topically in ophthalmology to induce mydriasis and cycloplegia. It has an advantage over atropine in that its duration of action is shorter (4–8 hours) (see also Chapter 14).

F. **Aminopentamide** (Centrine®)

1. **Therapeutic uses.** It is used orally, IM, or SC in dogs and cats for the treatment of **acute abdominal visceral spasm**, **pylorospasm or hypertrophic gastritis** and associated nausea, vomiting, and/or diarrhea. When compared with atropine as an anticholinergic drug, it has a greater effect on **reducing colonic contractions** and **less mydriatic and salivary effects.** Aminopentamide may **reduce gastric acid secretion** as well.
2. **Pharmacokinetics.** No information is available.

VII. GANGLIONIC NICOTINIC AGONISTS AND ANTAGONISTS.

Ganglionic nicotinic agonists and antagonists are of limited use in veterinary medicine. Skeletal neuromuscular junction nicotinic antagonists (see VIII) have more therapeutic uses.

A. Nicotine and nicotine-like antinematodal drugs, for example, levamisole, pyrantel, and morantel (see also Chapter 16).

1. **Mechanism of action (see Figure 2-1; Table 2-2)**
   - **a.** These compounds activate nicotinic receptors in both the sympathetic and parasympathetic ganglia, where they stimulate the postganglionic neuron. They mimic the actions of ACh in this aspect.
   - **b.** These compounds stimulate the adrenal medulla to release Epi and NE into the blood stream.
   - **c.** In the somatic nervous system, they stimulate the skeletal neuromuscular junction at nicotinic receptors.
2. **Pharmacologic effects**
   - **a. CNS.** Stimulation of the motor cortex by nicotine produces tremors.
   - **b. Respiratory.** Respiration may be initially stimulated and then depressed.
   - **c. Cardiovascular.** Increases in blood pressure, heart rate, and peripheral resistance result from stimulation of sympathetic ganglia and the adrenal medulla.
   - **d. Smooth muscle and glands.** Stimulation of parasympathetic ganglia may increase GI motility and salivary secretion.
3. **Therapeutic uses.** Nicotine has no therapeutic use, but **nicotine-like compounds are available as antiparasitic drugs.**
4. **Pharmacokinetics**
   - **a. Absorption.** Nicotine and nicotine-like compounds are well absorbed by all routes, including the dermal route.
   - **b. Metabolism.** They are metabolized by the liver via phase I and II metabolism.
   - **c. Excretion.** They are eliminated by the kidney both as metabolites and parent compound. The plasma $t_{1/2}$ of levamisole is 4–6 hours and of pyrantel tartrate is ~6 hours.
5. **Adverse effects**
   - **a.** Convulsions may occur with high doses.
   - **b.** Vomiting and muscle fasciculation may occur.
   - **c.** Depolarizing neuromuscular blockade paralyzes skeletal muscle, particularly respiratory muscle, which can be fatal.

B. Hexamethonium, trimethaphan, and mecamylamine are antagonists of post-ganglionic nicotinic receptors.

These drugs have been used as pharmacological tools to characterize nicotinic receptors in the ganglia, but have not been used in veterinary medicine. The primary disadvantage to their use is that they are **not selective** (i.e., they block transmission in both sympathetic and parasympathetic ganglia).

VIII. NEUROMUSCULAR BLOCKING DRUGS

A. Mechanism of action.

These drugs act on nicotinic receptors at neuromuscular junction (N_M receptors) via two different mechanisms to relax skeletal muscle.

1. **Depolarizing drugs** [e.g., succinyicholine (SuCh, Anectine®)]. SuCh acts like ACh to depolarize the neuromuscular junction, but it is hydrolyzed by AChE less rapidly. Solutions of SuCh should always be kept cold in the field, since it undergoes spontaneous hydrolysis.
   - **a. Phase I.** The nonselective cation channel associated with the N_M receptor is opened and the receptor is depolarized. Persistent binding of succinylcholine to the N_M receptor transforms the receptor so that it is incapable of transmitting further impulses. This phase is associated with **muscle fasciculation**.

TABLE 2-4. Duration of Action of Competitive N_M Blockers When Administered IV

	Tuborcurarine		Pancuronium		Atracurium		Vecuronium	
Animal	**Dose (mg/kg)**	**Duration (min)**	**Dose (mg/kg)**	**Duration (min)**	**Dose (mg/kg)**	**Duration (min)**	**Dose (mg/kg)**	**Duration (min)**
Horse	0.3	60	0.06	40	0.15	30	0.1	30
Cow	0.06	30	0.04	40	—	—	—	—
Sheep	0.04	30	0.025	45	0.5	30	0.04	15
Pig	0.4	30	0.1	30	—	—	—	—
Dog	—	—	0.06	30	0.5	40	0.1	25
Cat	—	—	—	—	0.5	40	0.1	25

Modified from Table 2-4, *NVMS Pharmacology*.

   b. Phase II. Over time, the nonselective cation channel closes and repolarization occurs, rendering the neuromuscular junction resistant to depolarization. Flaccid paralysis ensues.

2. **Competitive blocking drugs** (e.g., tubocurarine, pancuronium, atracurium, vecuronium)—nondepolarizing drugs. These drugs occupy the N_M receptor but do not activate it. By reducing the number of N_M receptors available for ACh, the end-plate potential is reduced, the threshold required to excite the muscle is not reached, and the muscle relaxes.

B. Pharmacokinetics

1. **Depolarizing drugs**
   a. Following IV or IM administration (IV is preferred), SuCh has a rapid onset of action. Since there is a species difference in the level of pseudocholinesterase, the duration of action varies according to species and dosages. Ruminants have lower levels of this enzyme than other species, that is, horses. For unknown reasons, dogs may show prolonged paralysis after SuCh administration.
   b. SuCh is hydrolyzed by pseudocholinesterase of liver and plasma. Animals that have been exposed to an organophosphate cholinesterase inhibitor (e.g., in ectoparasiticides or eyedrops) up to 30 days before SuCh administration may experience a prolonged duration of action caused by a reduced rate of hydrolysis.
2. **Competitive blocking drugs**. Each drug has a specific duration of action that varies according to species following IV administration (Table 2-4).
   a. Tubocurarine is not significantly metabolized in animals. Approximately 50% is excreted unchanged in the urine and 50% in the bile. Caution should be taken not to administer tubocurarine to animals with liver or kidney disease.
   b. Pancuronium is metabolized by the liver, but the kidney is the major route for elimination.
   c. Atracurium has a unique mechanism for metabolism. It undergoes spontaneous degradation in the plasma called Hoffman elimination and ester hydrolysis, which do not involve the liver or kidneys. Thus, in patients with renal or liver disease, atracurium may be the drug of choice for relaxing skeletal muscle.
   d. Vecuronium is eliminated by the kidney (~15%) and by metabolism and biliary excretion.

C. Therapeutic uses. Neuromuscular blockers are used to

1. Promote and enhance skeletal muscle relaxation during surgery. This permits less general anesthetic to be used and enhances safety of the surgery.
2. Facilitates endotracheal intubation.

D. Adverse effects

1. **General aspects**
   - **a.** These drugs do not affect sensory mechanisms. Though paralyzed, conscious animals still feel pain.
   - **b.** Prolonged apnea may occur.
   - **c.** These drugs should not be used unless facilities are available for administering artificial respiration.
2. **Succinylcholine**
   - **a.** Succinylcholine elicits uncoordinated muscle contraction that may last for ~30 seconds and be painful. ACh receptors in autonomic ganglia and muscarinic receptors may be stimulated by SuCh. This may result in bradycardia and increases in bronchiolar and salivary secretion.
   - **b.** SuCh may serve as a trigger for malignant hyperthemia in the pig and horse.
3. **Tubocurarine** may reduce blood pressure by causing histamine release and by blocking transmission in autonomic ganglia. Dogs and cats are prone to histamine release by tubocurarine, which precludes its use in these species. Histamine release may also cause bronchospasm, bronchial secretion, and salivation.
4. **Pancuronium** causes a small increase in heart rate.
5. **Atracurium** does induce histamine release but the extent of release is less than that of tubocurarine.
6. **Vecuronium** does not have other adverse effects.

E. Factors influencing the action of neuromuscular blocking drugs

1. Genetic or ChE inhibitor-induced decreases in plasma. ChE activity will prolong the duration of action of SuCh.
2. Hepatic disease may prolong the duration of action of SuCh, since the liver synthesizes plasma ChE.
3. Aminoglycoside antibiotics have neuromuscular blocking activities since they inhibit ACh release.
4. Inhalant anesthetics, for example, isoflurane, enhance nondepolarizing neuromuscular blockade since they stabilize the postjunctional membrane.
5. Concomitant administration of SuCh with inhalation anesthetics may induce increased incidences of bradycardia, arrhythmias, sinus arrest, and apnea (owing to ganglionic blockade).

F. Reversal of neuromuscular blockade

1. Competitive neuromuscular blockers can be antagonized by ChE inhibitors such as edrophonium and neostigmine.
2. No good antagonists exist for SuCh. The patient should be ventilated until recovery occurs.

SUGGESTED READING

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