Human Phys PCB4701

Autonomic Nervous System
Fox Chapter 9 part 1

Anatomy and Neurochemistry of Autonomic Nervous System

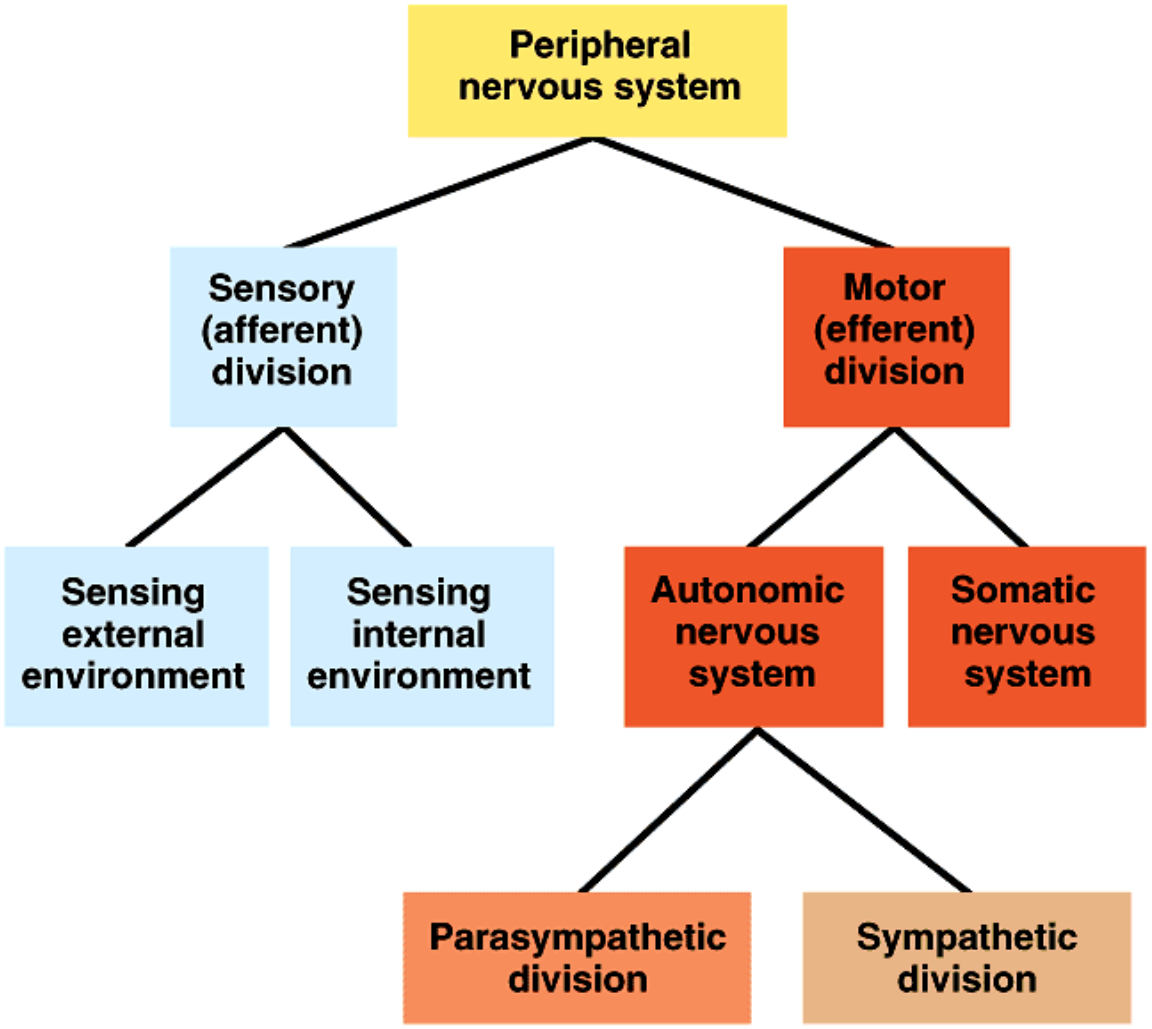
Pharmacology and Disorders of Autonomic Nervous System

Fox Table 9.1

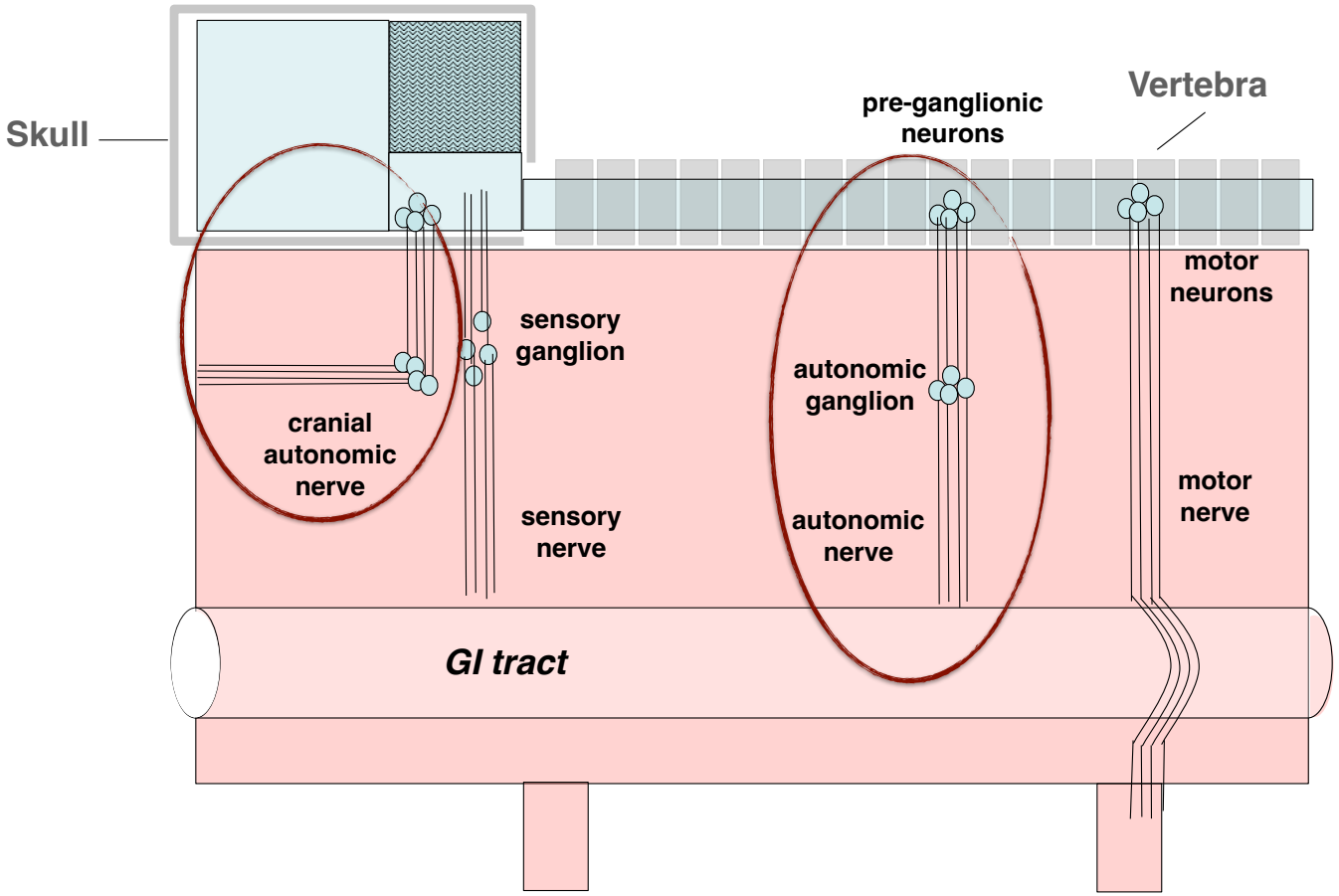
Table 9.1 | Comparison of the Somatic Motor System and the Autonomic Motor System

Feature	Somatic Motor	Autonomic Motor
Effector organs	Skeletal muscles	Cardiac muscle, smooth muscle, and glands
Presence of ganglia	No ganglia	Cell bodies of postganglionic autonomic fibers located in paravertebral, prevertebral (collateral), and terminal ganglia
Number of neurons from CNS to effector	One	Two
Type of neuromuscular junction	Specialized motor end plate	No specialization of postsynaptic membrane; all areas of smooth muscle cells contain receptor proteins for neurotransmitters
Effect of nerve impulse on muscle	Excitatory only	Either excitatory or inhibitory
Type of nerve fibers	Fast-conducting, thick (9–13μm), and myelinated	Slow-conducting; preganglionic fibers lightly myelinated but thin (3μm); postganglionic fibers unmyelinated and very thin (about 1.0μm)
Effect of denervation	Flaccid paralysis and atrophy	Muscle tone and function persist; target cells show denervation hypersensitivity

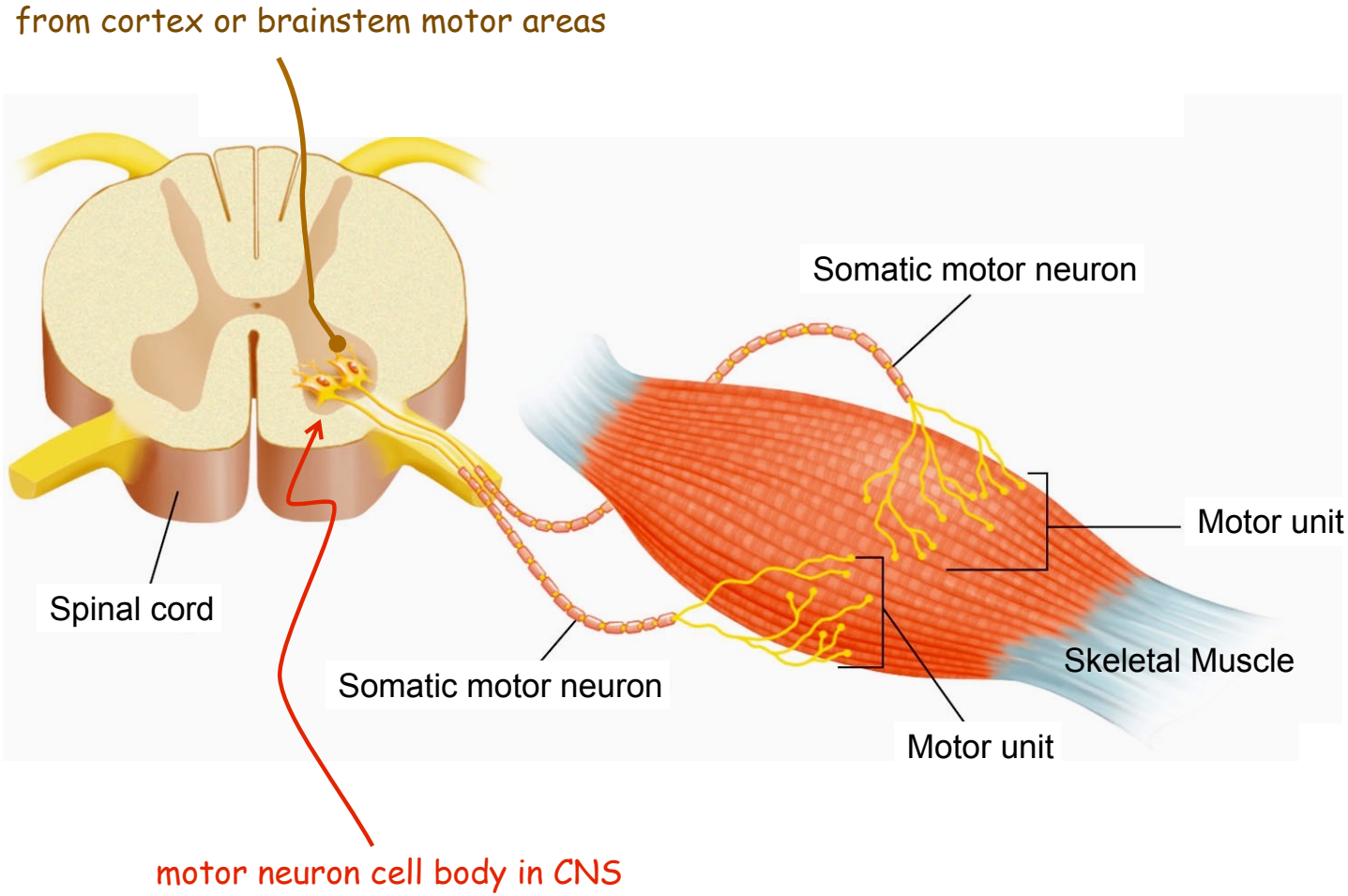
Functional hierarchy of the peripheral nervous system



Autonomic Nervous System



Somatic Motor System (voluntary):
Spinal motor neuron synapses onto target skeletal muscle

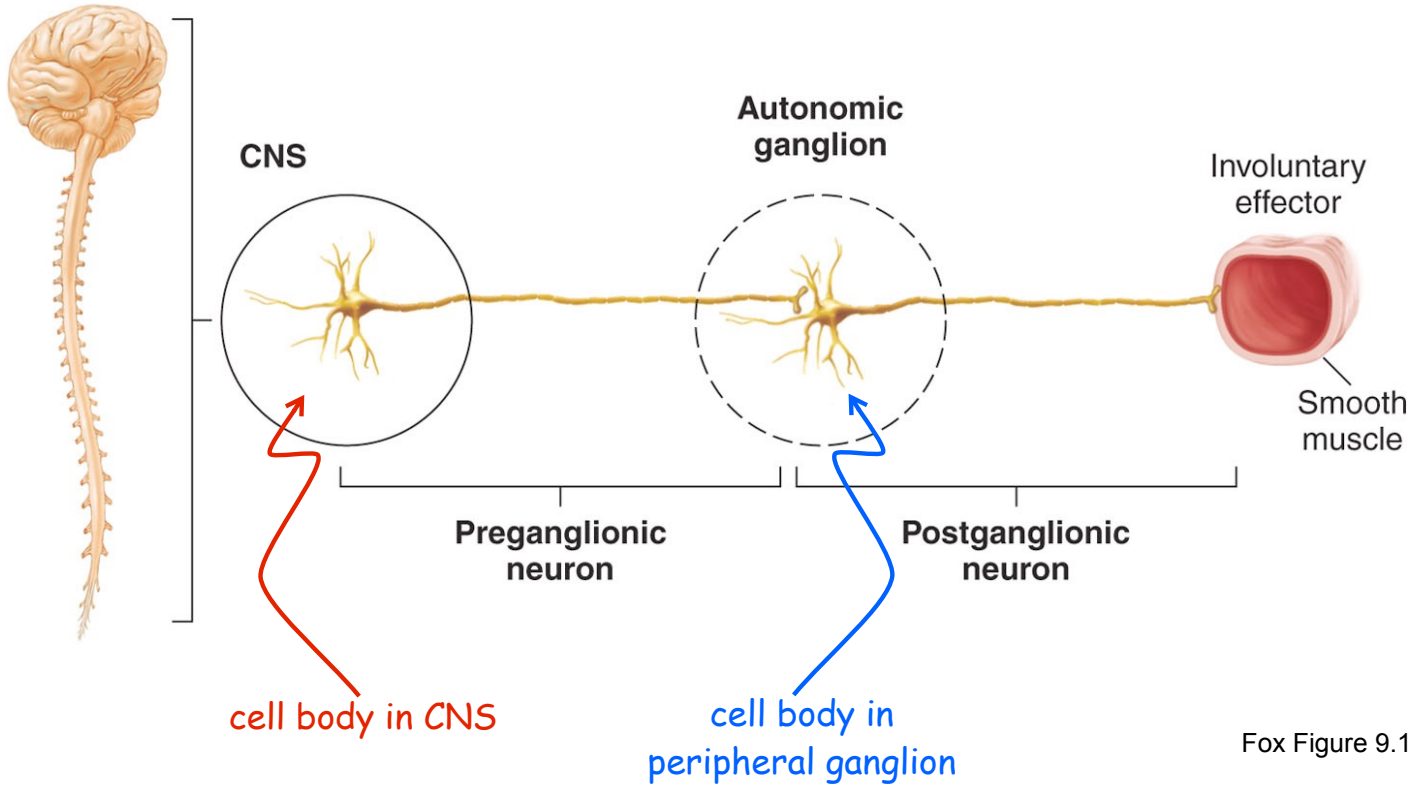


Fox Figure 12.4a

Autonomic Nervous System (involuntary):

Two-Step Projection:

1. Spinal/Brainstem pre-ganglionic neuron synapses onto post-ganglionic neuron
2. Post-ganglionic neuron synapses onto target smooth muscle
   (e.g. in blood vessel, glands)



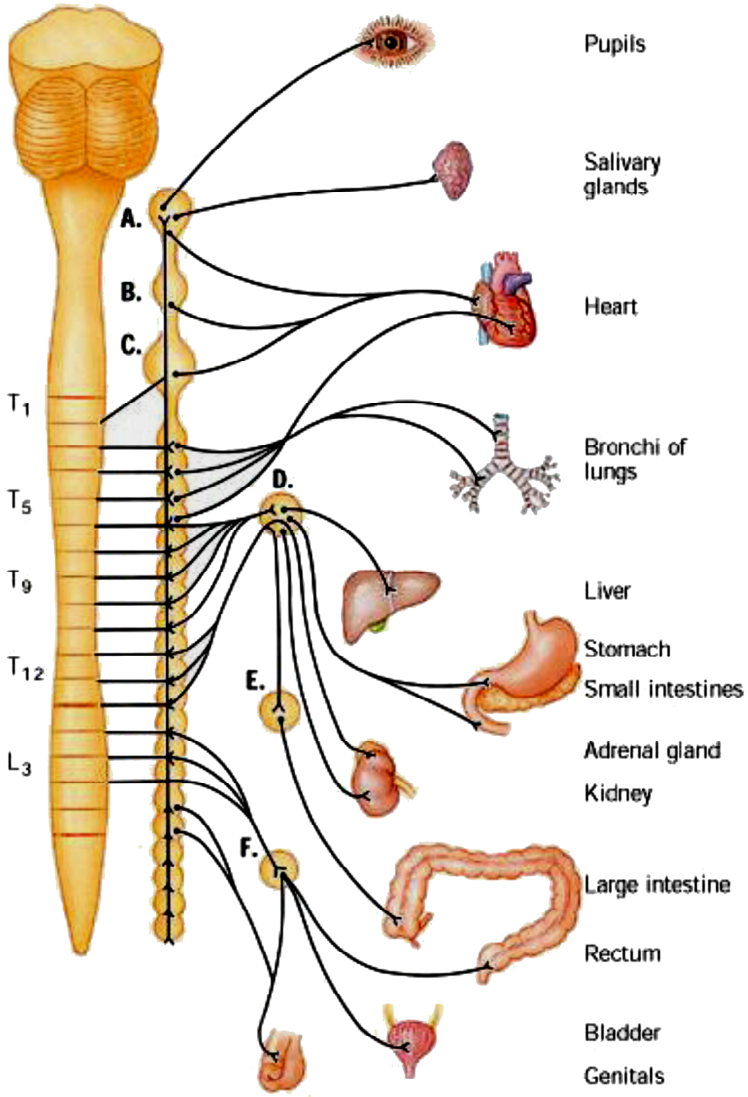
Fox Figure 9.1

Sympathetic Nervous System

Nerves from spinal cord run to chain ganglia or collateral ganglia and then to glands and smooth muscle

mobilize energy
divert blood to muscle
prepare to fight/flee

"Fight or Flight"



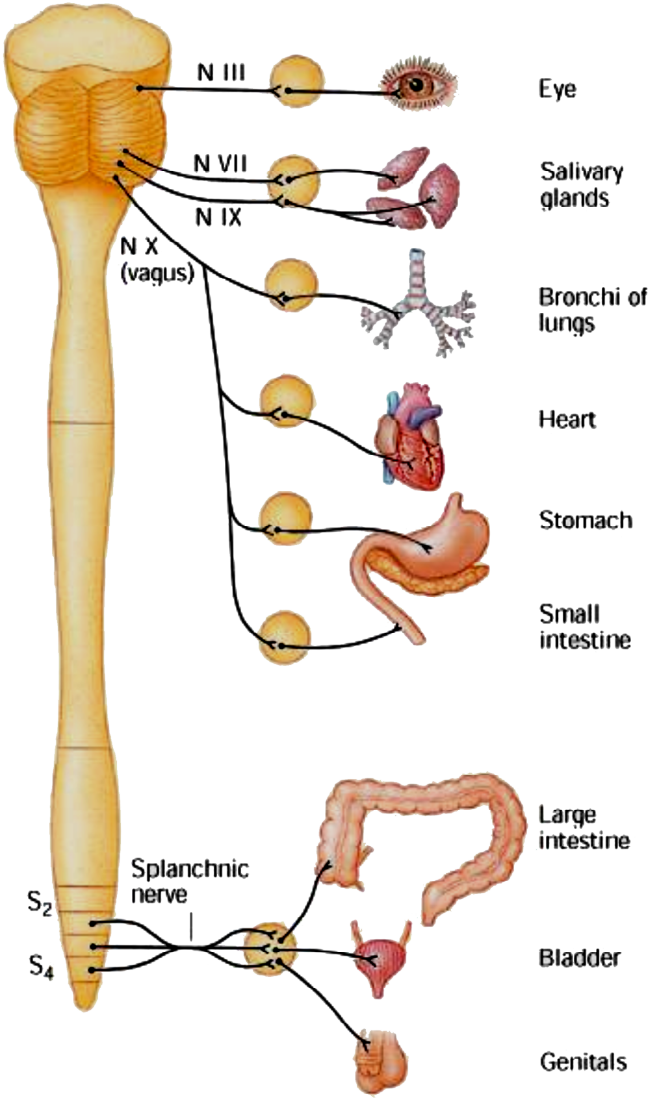
Parasympathetic Nervous System

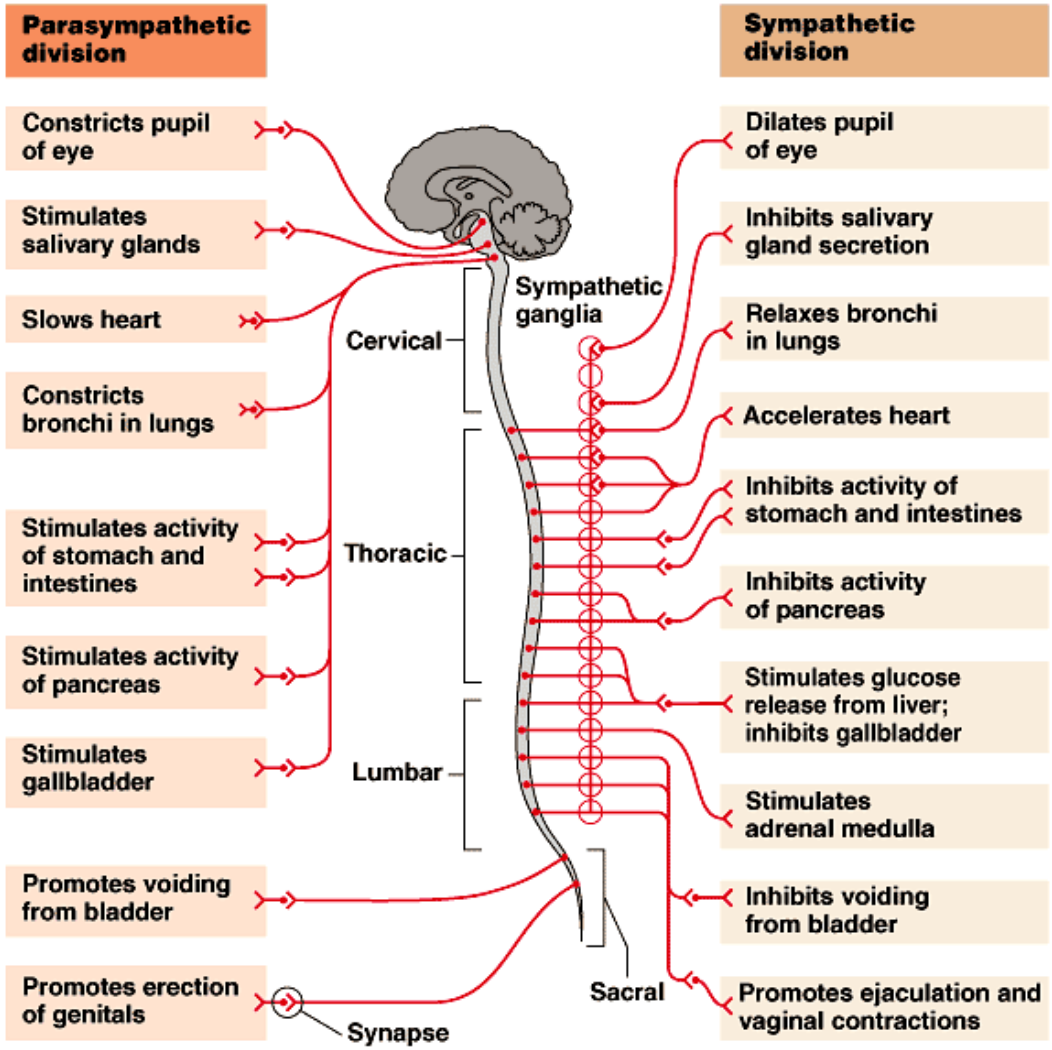
Nerves from brainstem and spinal cord run to glands and smooth muscle

Prepare for digestion, energy storage, divert blood flow to gut.

opposite effect of sympathetic NS (in most cases)

"Rest and Digest"





Comparison of Skeletal Muscle and Smooth Muscle

Skeletal Muscle	Smooth Muscle
Striated; actin and myosin arranged in sarcomeres	Not striated; more actin than myosin; actin inserts into dense bodies and cell membrane
Well-developed sarcoplasmic reticulum and transverse tubules	Poorly developed sarcoplasmic reticulum; no transverse tubules
Contains troponin in the thin filaments	Contains calmodulin, a protein that, when bound to Ca^{2+}, activates the enzyme myosin light-chain kinase
Ca^{2+} released into cytoplasm from sarcoplasmic reticulum	Ca^{2+} enters cytoplasm from extracellular fluid, sarcoplasmic reticulum, and perhaps mitochondria
Cannot contract without nerve stimulation; denervation results in muscle atrophy	Maintains tone in absence of nerve stimulation; visceral smooth muscle produces pacemaker potentials; denervation results in hypersensitivity to stimulation
Muscle fibers stimulated independently; no gap junctions	Gap junctions generally present

attached to tendons and bones;
contracts to move skeleton.

receptors at neuromuscular junction

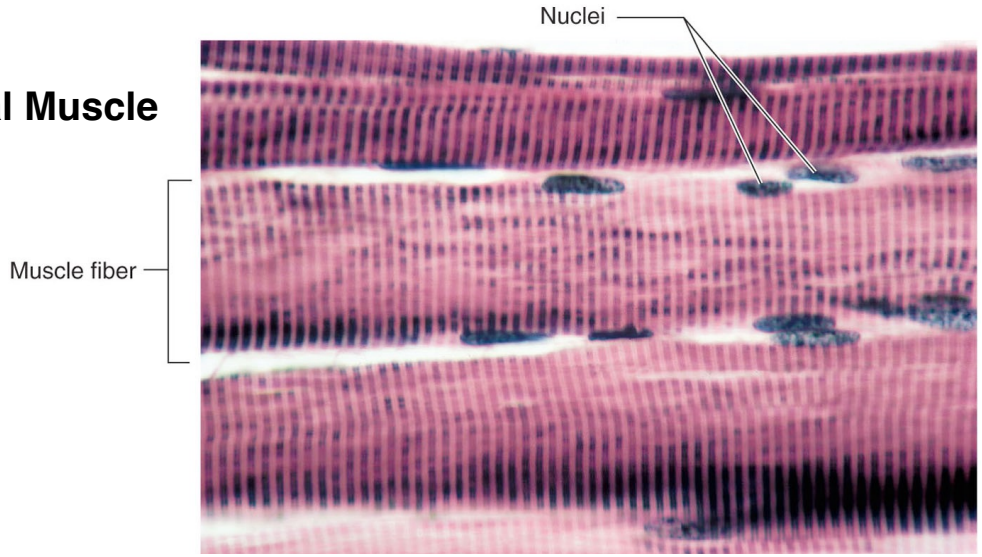
wrapped around blood vessels, GI tract, glands;
contracts to constrict vessels or squeeze glands.

neurotransmitter receptors all over cell surface

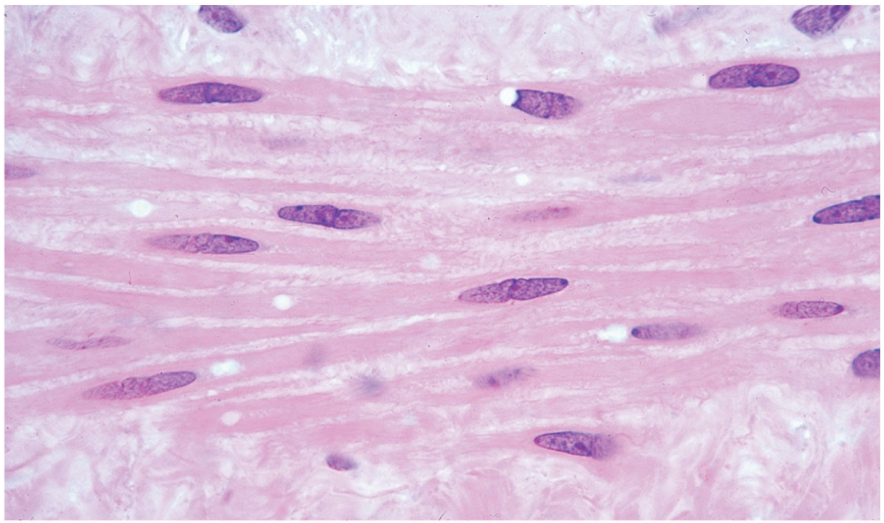
Fox Table 12.8

Fox Figure 12.35a

Skeletal Muscle



Smooth Muscle



(a)

Figure 12.35b

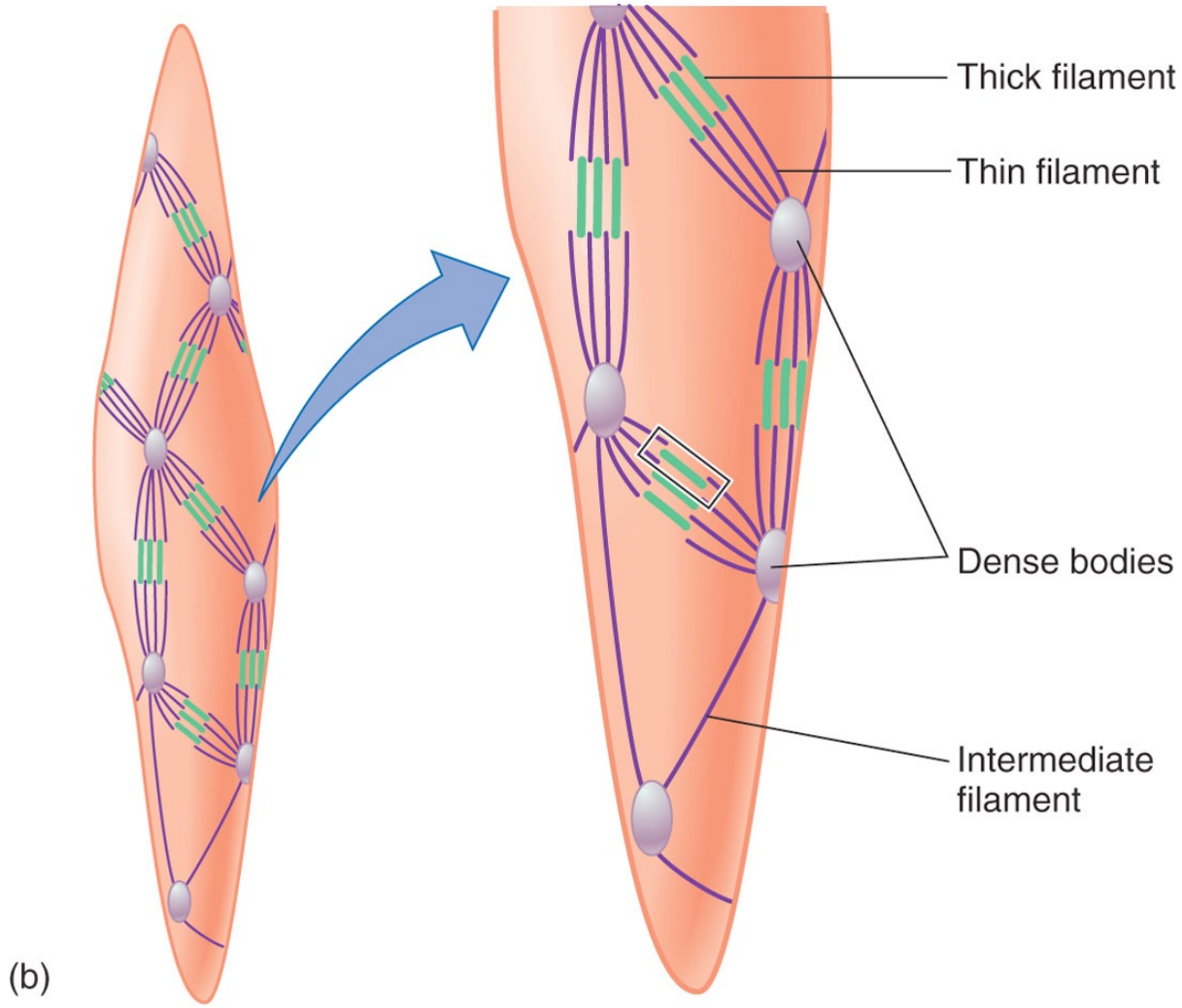


Figure 12.35c

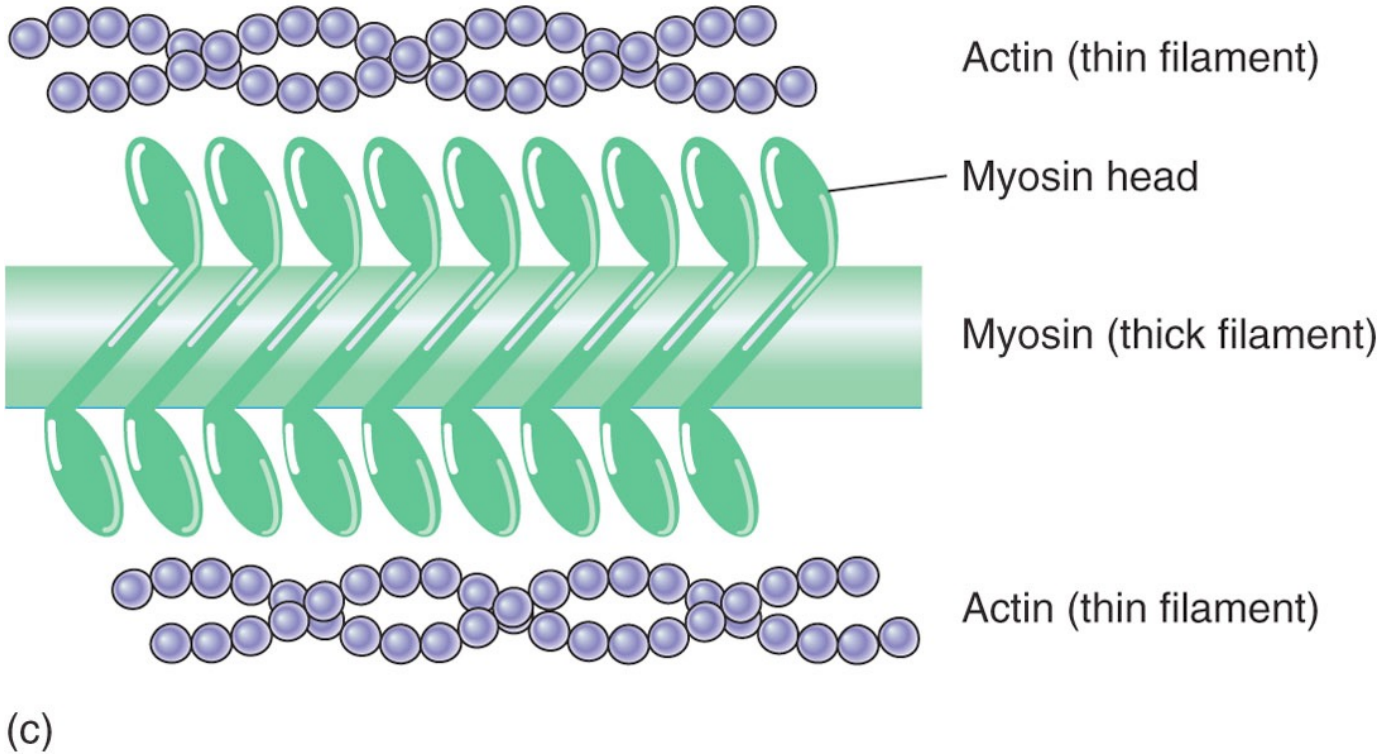
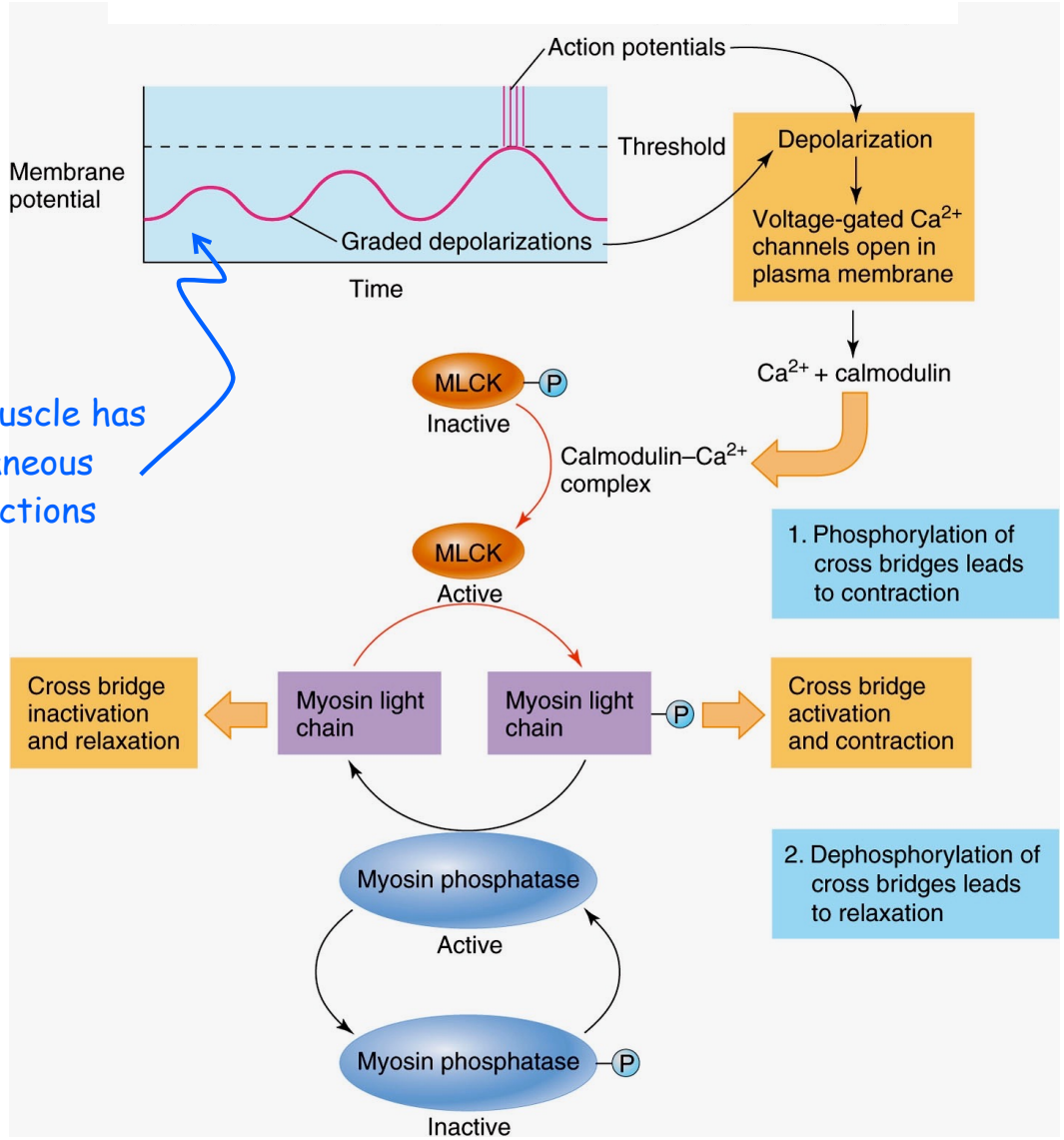


Figure 12.36



smooth muscle has spontaneous contractions

Sympathetic Nervous System: Anatomy

Sympathetic chain of paravertebral ganglia

- connected to spinal roots by **white ramus** (preganglionic going into ganglion) and **gray ramus** (postganglionic leaving out of ganglion)
- convergence of inputs leads to **mass activation** of postganglionic neurons
- postganglionic fibers join **spinal nerves**, innervate blood vessels et al. in skeletal muscles and skin.

Splanchnic Nerves

- Sympathetic preganglionic fibers below the diaphragm project to **collateral ganglia**
- Postganglionic fibers from collateral ganglia innervate digestive, urinary, reproductive organs

Medulla of Adrenal Gland

- modified sympathetic ganglion
- Preganglionic fibers stimulate medullary cells to secrete epinephrine and norepinephrine into the blood

Neurotransmitters

- Preganglionic nerves release **Acetylcholine (ACh)** to stimulate **nicotinic receptors** on postganglionic cells
- Postganglionic cells release **Norepinephrine (NE)** to stimulate or inhibit target tissues via **adrenergic receptors**
- There are some important exceptions: e.g. sympathetic fibers to sweat glands use ACh.
-

ramus - Latin for branch
splan - Greek for organ
medulla - Latin for middle

Autonomic Nervous System Transmitters and Receptors

Acetylcholine -> Cholinergic Receptors

- Nicotinic (ligand gated Na+ channels)
- Muscarinic (G-protein-coupled receptors)

Norepinephrine -> Adrenergic Receptors

(Epinephrine from adrenal gland)

- alpha-adrenergic receptors (G-protein-coupled receptors)
- beta-adrenergic receptors (G-protein-coupled receptors)

Sympathetic Nervous System: Anatomy

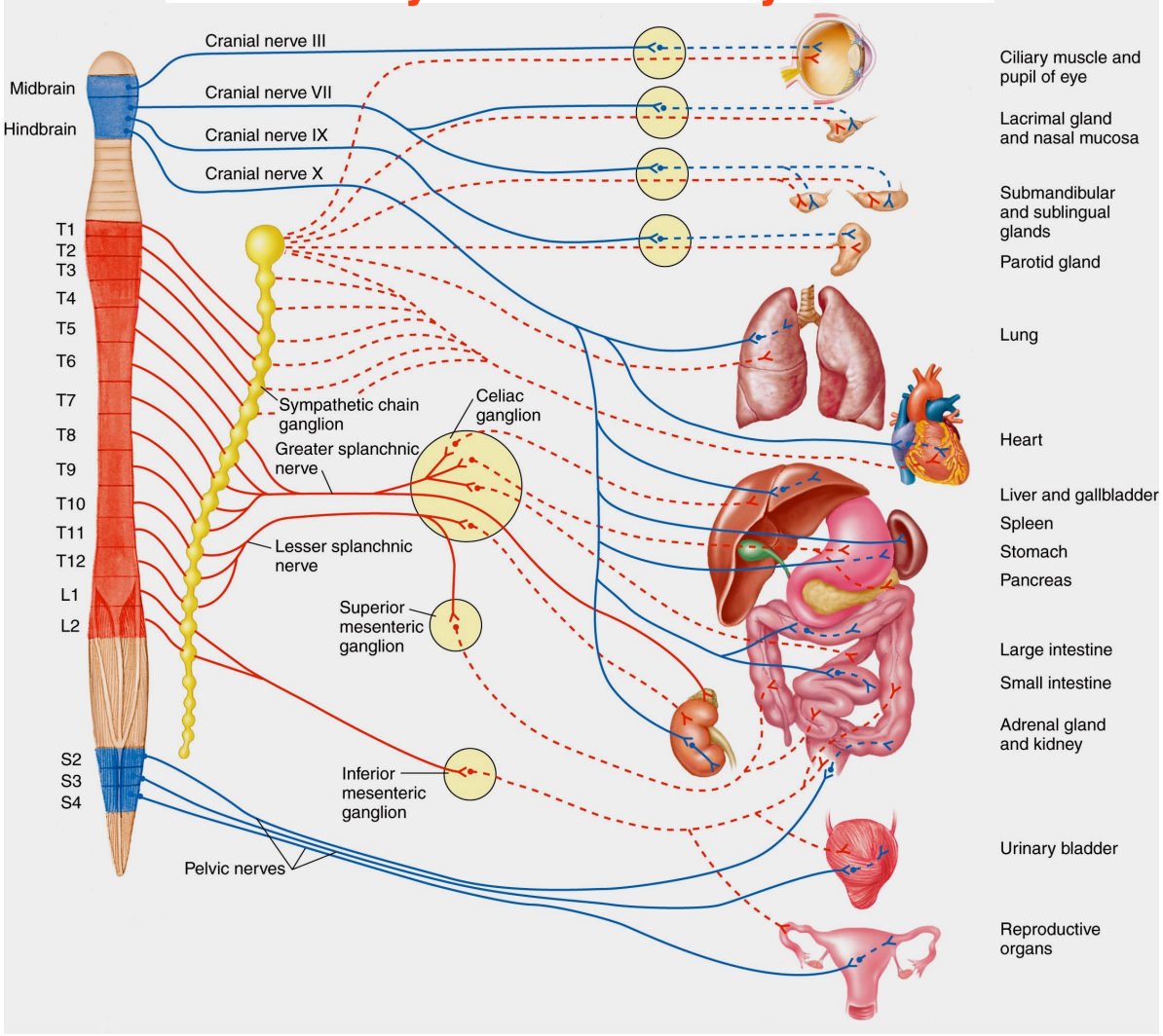


Figure 9.5

Sympathetic Nervous System: Anatomy

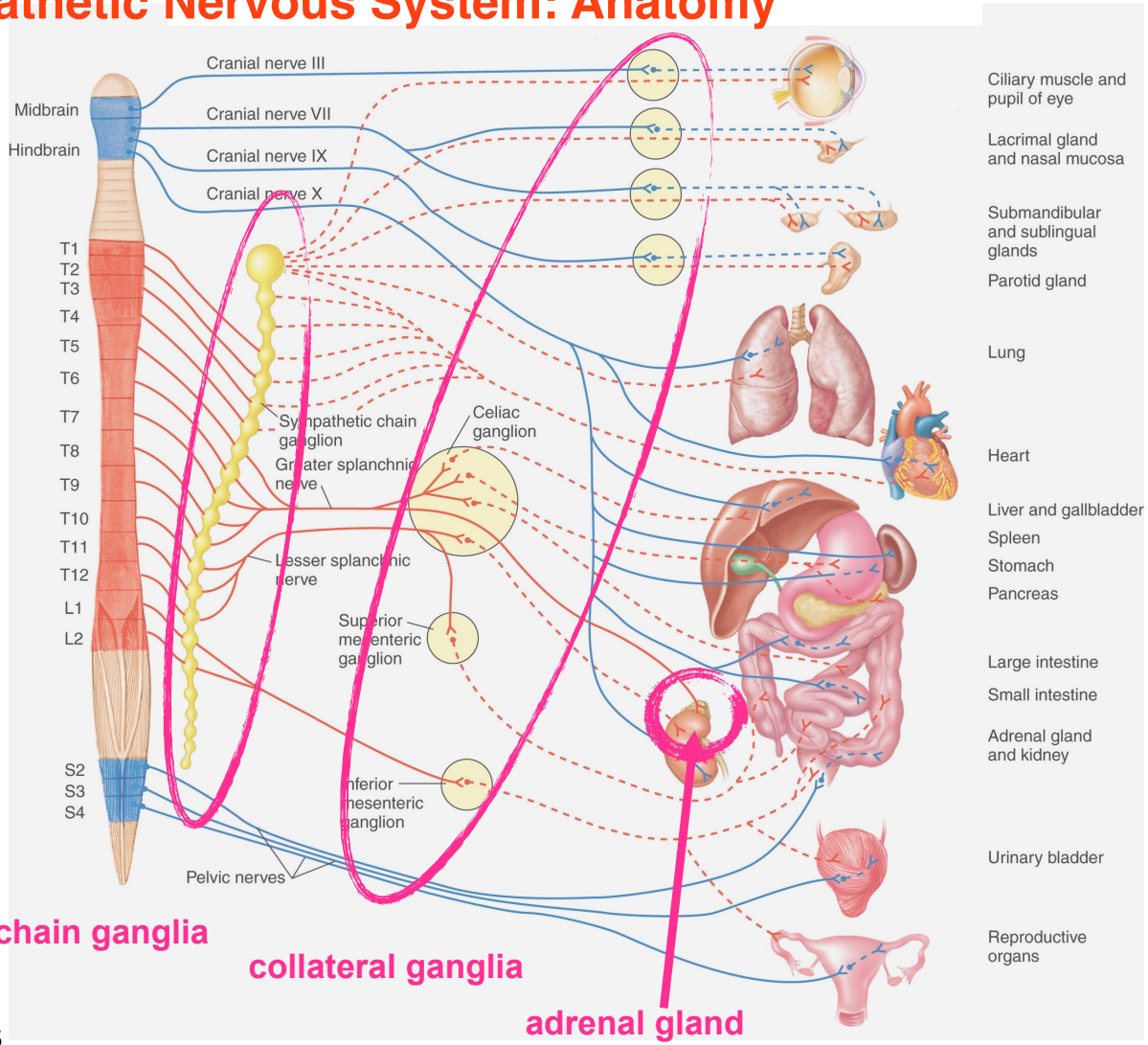
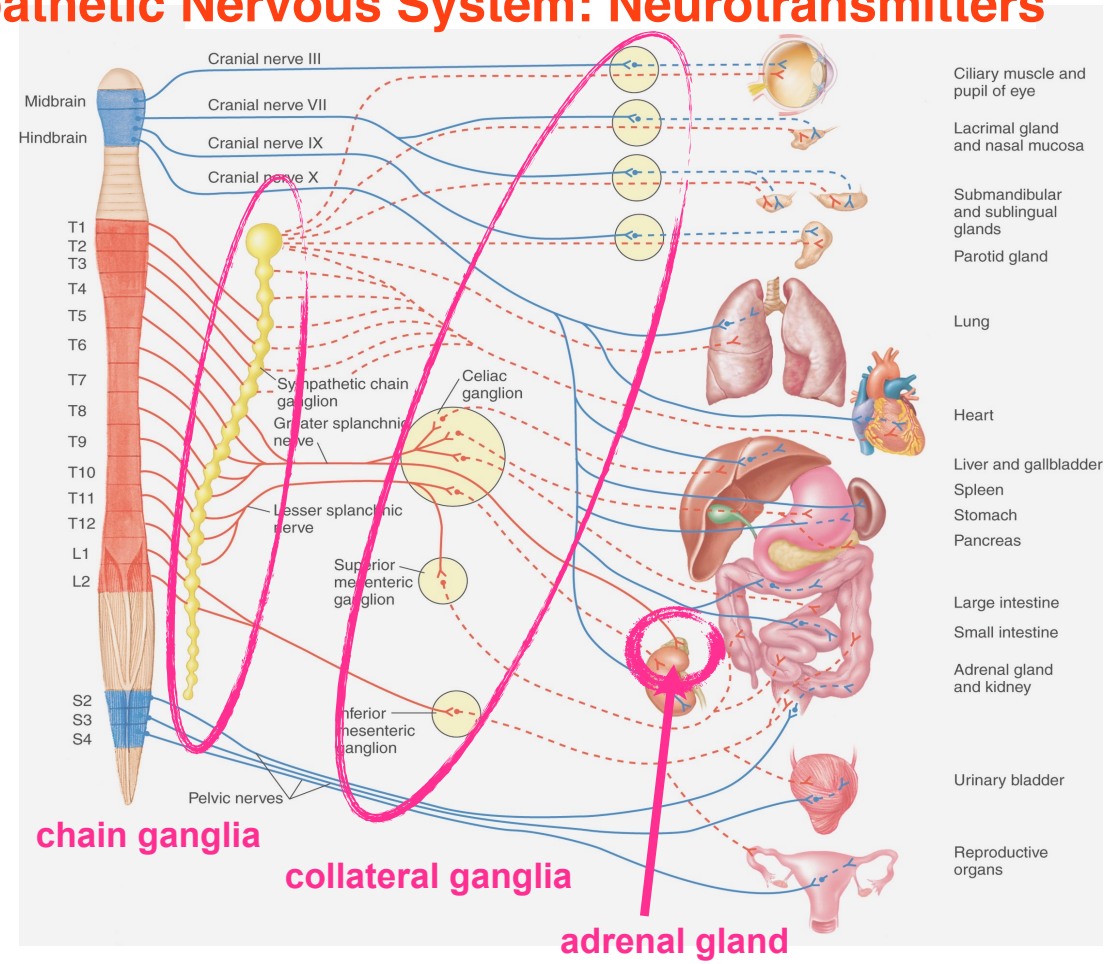


Figure 9.5

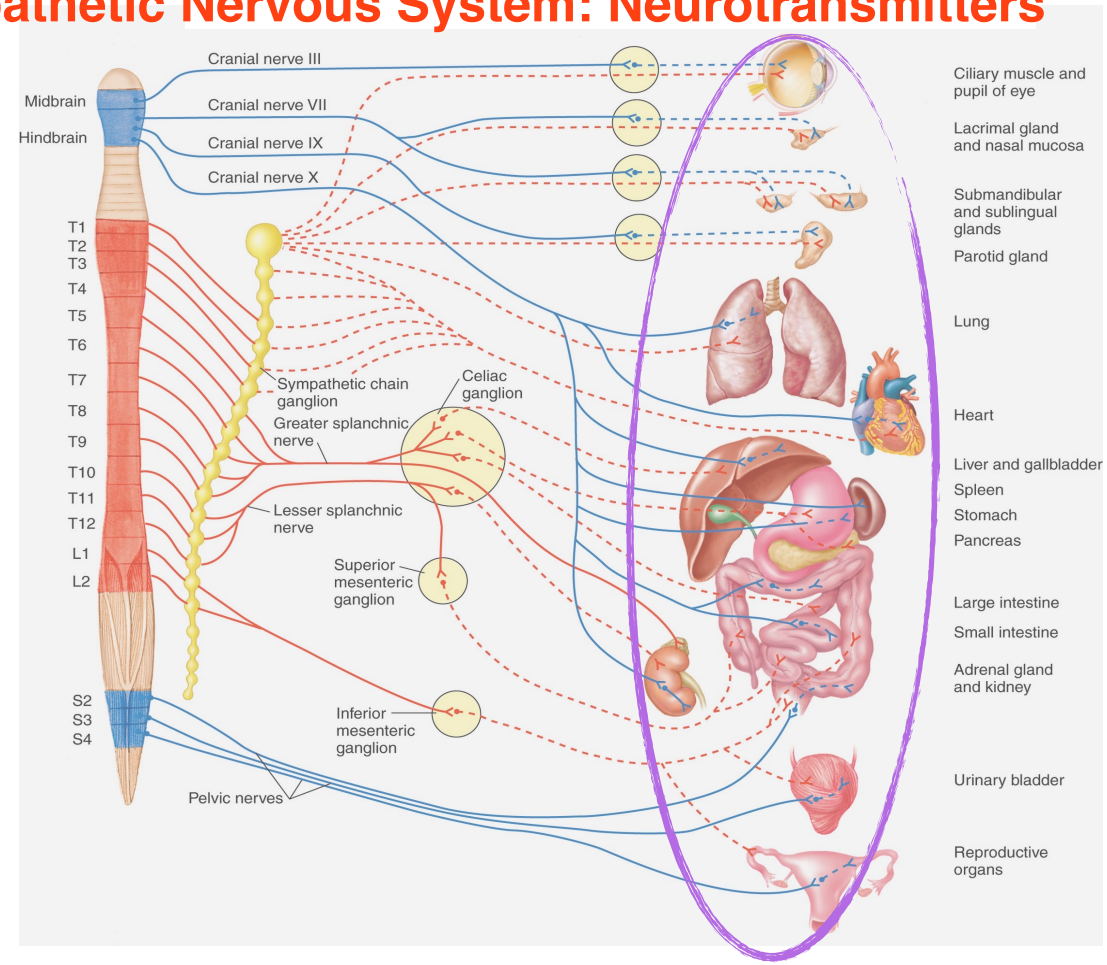
Sympathetic Nervous System: Neurotransmitters



Ach -> nicotinic receptors in ganglion

Figure 9.5

Sympathetic Nervous System: Neurotransmitters



NorEpi -> beta and alpha noradrenergic receptors at target organ

Figure 9.5

Sympathetic Nervous System: Neurotransmitters

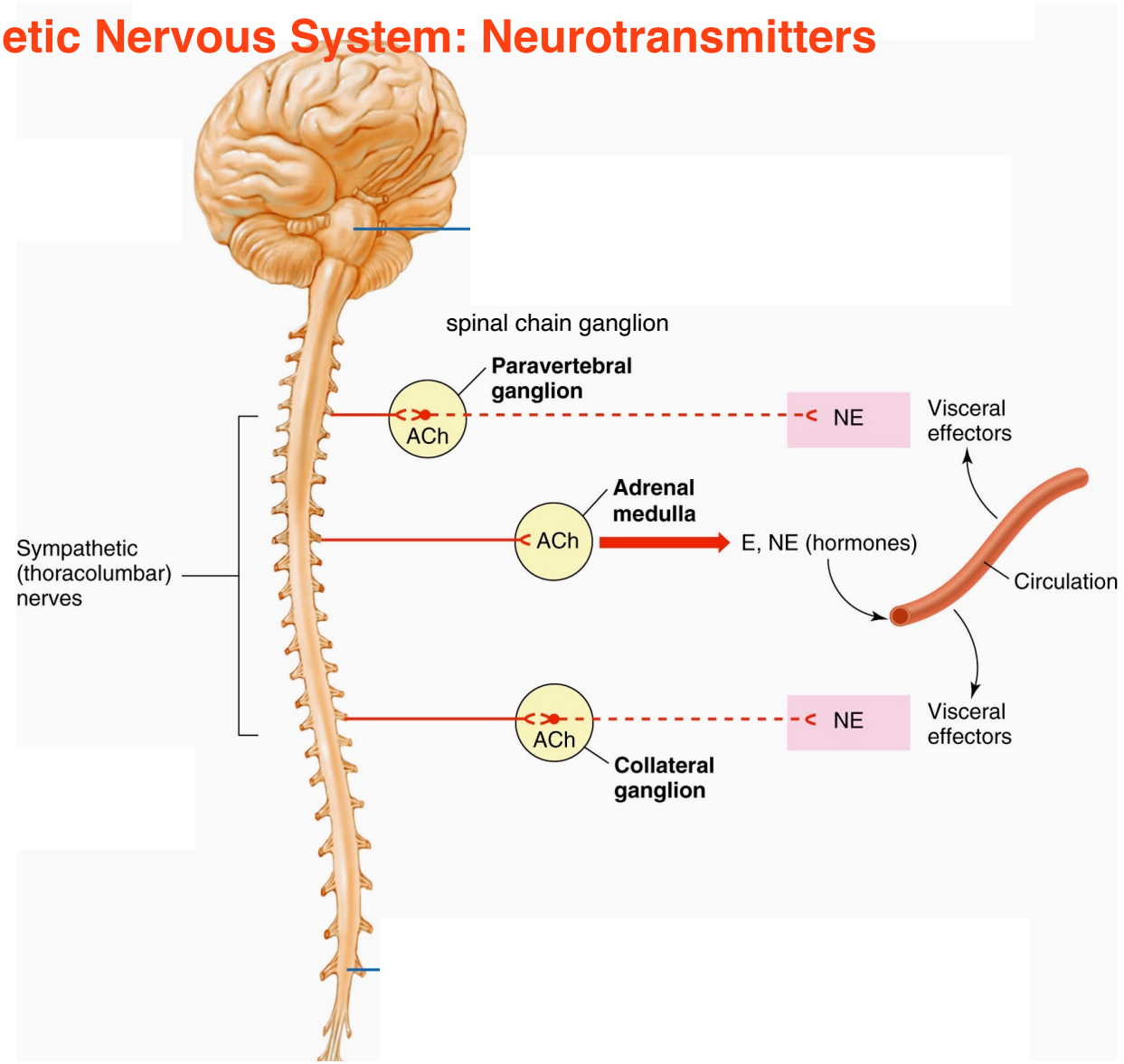


Figure 9.7

Table 9.3

Table 9.3 | The Parasympathetic Division

Nerve	Origin of Preganglionic Fibers	Location of Terminal Ganglia	Effector Organs
Oculomotor (third cranial) nerve	Midbrain (cranial)	Ciliary ganglion	Eye (smooth muscle in iris and ciliary body)
Facial (seventh cranial)	Pons (cranial)	Pterygopalatine and submandibular ganglia	Lacrimal, mucous, and salivary glands
Glossopharyngeal (ninth cranial) nerve	Medulla oblongata (cranial)	Otic ganglion	Parotid gland
Vagus (tenth cranial) nerve	Medulla oblongata (cranial)	Terminal ganglia in or near organ	Heart, lungs, gastrointestinal tract, liver, pancreas
Pelvic spinal nerves	S2 to S4 (sacral)	Terminal ganglia near organs	Lower half of large intestine, rectum, urinary bladder, and reproductive organs

Parasympathetic Nervous System: Anatomy

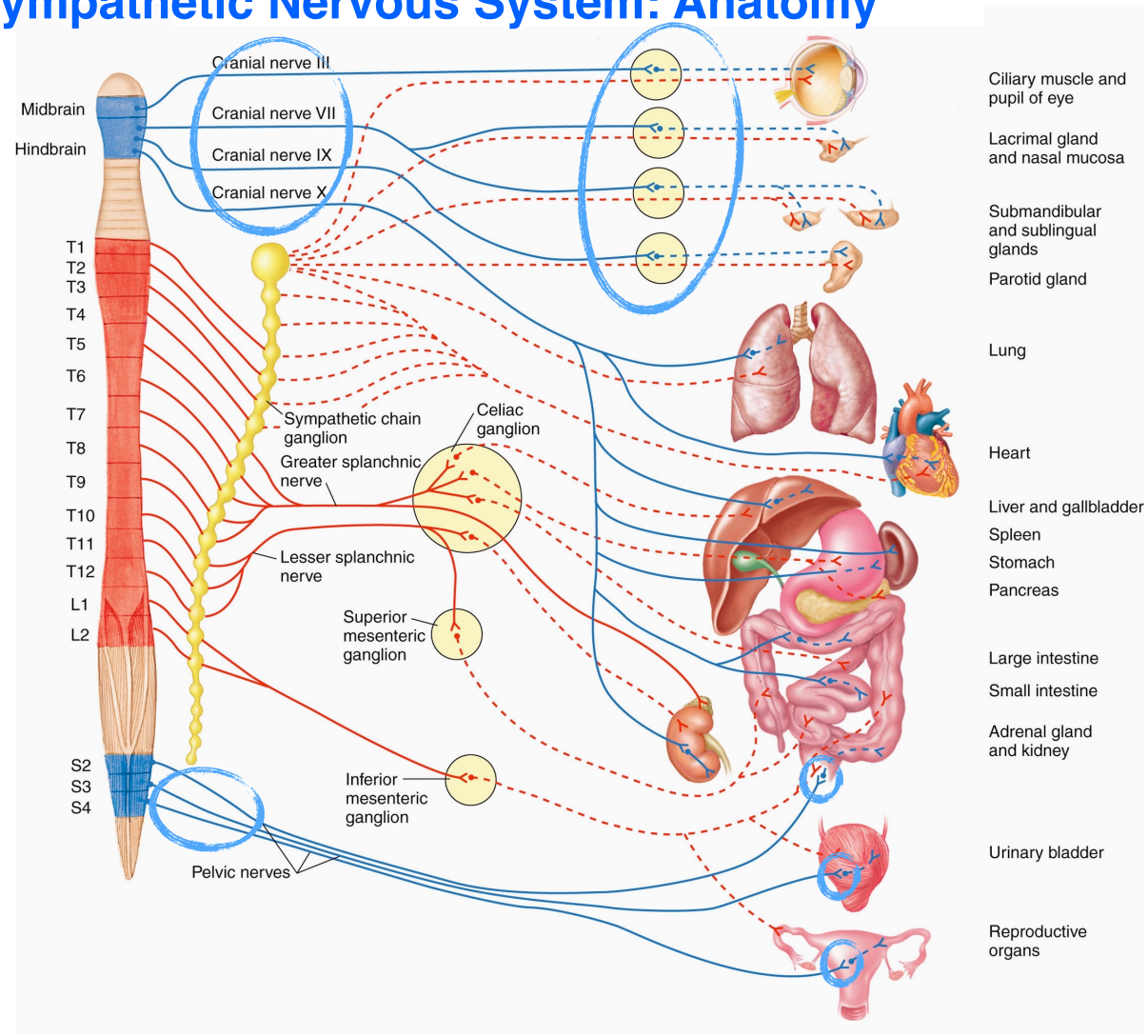


Figure 9.5

Parasympathetic Nervous System: Neurotransmitters

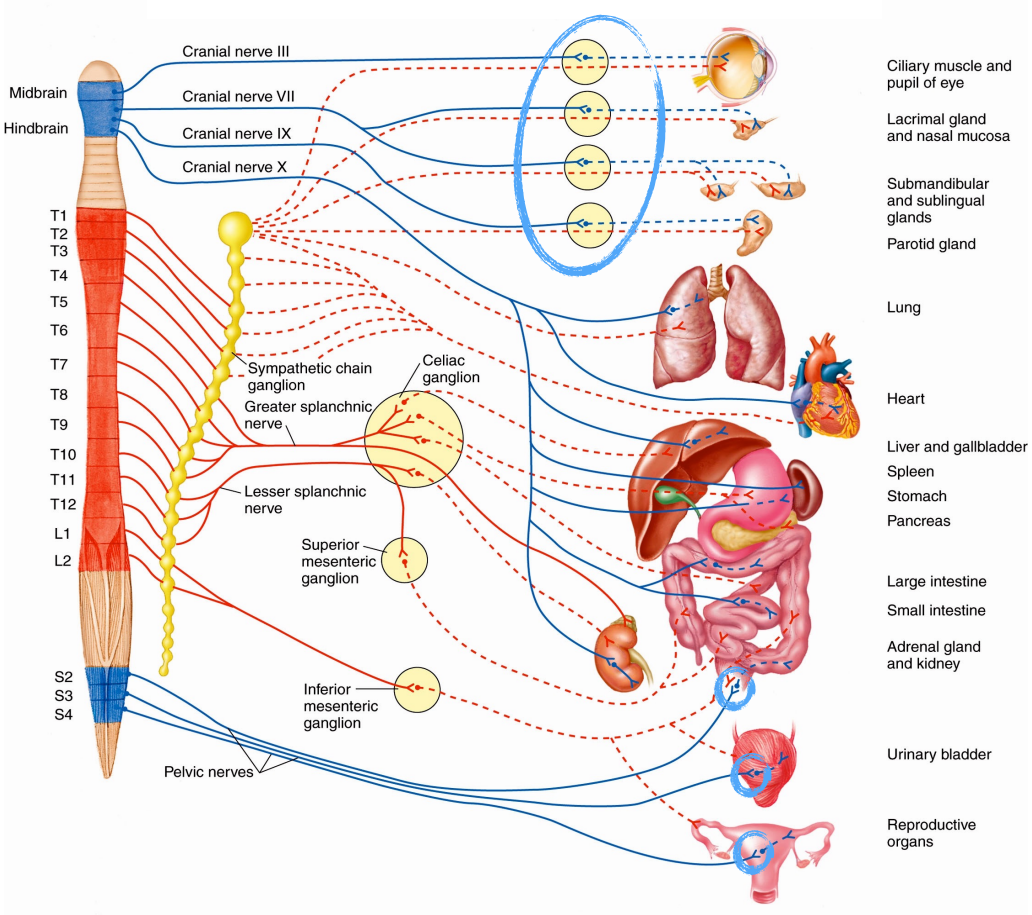


Figure 9.5

ACh -> Nicotinic Receptors at ganglion

Parasympathetic Nervous System: Neurotransmitters

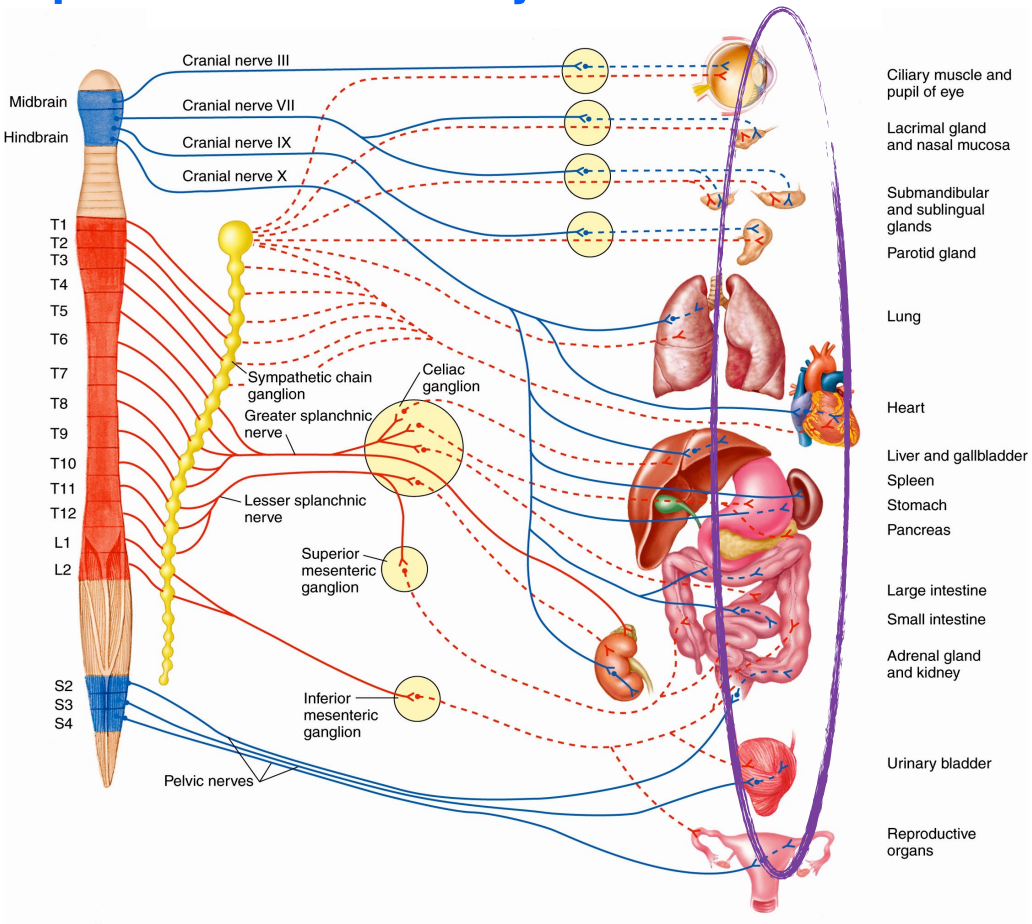


Figure 9.5

ACh -> Muscarinic Receptors at Target Organs

Parasympathetic Nervous System: Neurotransmitters

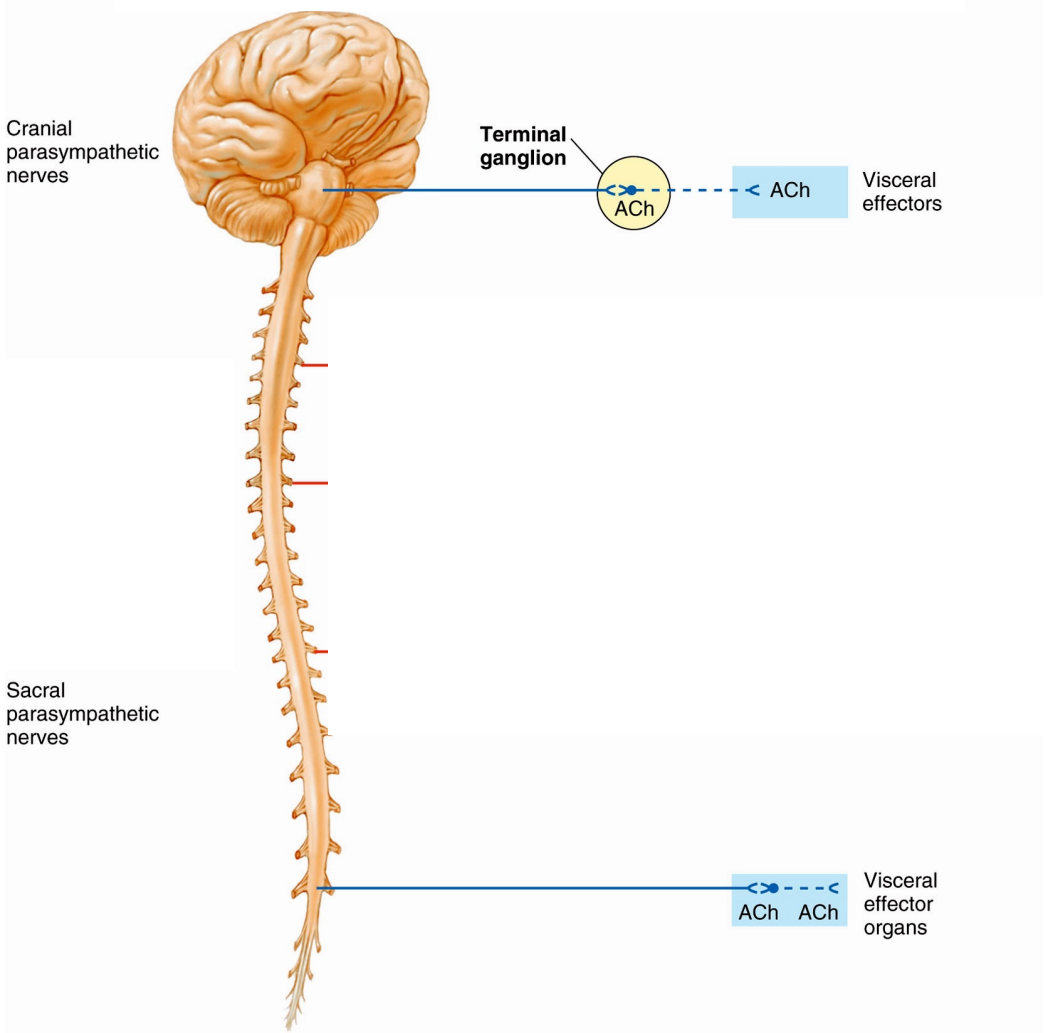


Figure 9.7

Autonomic Nervous System: Neurochemistry

- Both sympathetic and parasympathetic preganglionic neurons release ACh to stimulate **nicotonic receptors** on postganglionic cells
  *nicotinic receptors are blocked by **curare***

- Parasympathetic postganglionic neurons release ACh onto **muscarinic receptors**
  *muscarinic receptors are blocked by **atropine*** *belladona extract*
  muscanic receptors are G-protein-coupled receptors that have stimulatory or inhibitory effects on target organ, depending on the specific receptor subtype (M1-5)

- Sympathetic postganglionic neurons release NE (mostly) onto **adrenergic receptors**
  adrenergic receptors are G-protein-coupled receptors that have stimulatory or inhibitory effects on target organ, depending on the receptor subtype (alpha or beta)
  *adrenergic receptors are blocked by **alpha blockers** or **beta blockers.***

- Most target organs have **dual innervation** by sympathetic and parasympathetic fibers. The effects are usually **antagonistic** (but can be complementary, or cooperative).

- Some organs receive **only sympathetic innervation**: adrenal medulla, skin (arrector pili & sweat glands), and most blood vessels.

Table 9.4

Table 9.4 | Effects of Autonomic Nerve Stimulation on Various Effector Organs

Effector Organ	Sympathetic Effect	Parasympathetic Effect
Eye		
Iris (radial muscle)	Dilation of pupil	—
Iris (sphincter muscle)	—	Constriction of pupil
Ciliary muscle	Relaxation (for far vision)	Contraction (for near vision)
Glands		
Lacrimal (tear)	—	Stimulation of secretion
Sweat	Stimulation of secretion	—
Salivary	Saliva becomes thick	Increased secretion; saliva becomes thin
Stomach	—	Stimulation of secretion
Intestine	—	Stimulation of secretion
Adrenal medulla	Stimulation of hormone secretion	—
Heart		
Rate	Increased	Decreased
Conduction	Increased rate	Decreased rate
Strength	Increased	—
Blood Vessels	Mostly constriction; affects all organs	Dilation in a few organs (e.g., penis)
Lungs		
Bronchioles (tubes)	Dilation	Constriction
Mucous glands	Inhibition of secretion	Stimulation of secretion
Gastrointestinal Tract		
Motility	Inhibition of movement	Stimulation of movement

Table 9.4 | Effects of Autonomic Nerve Stimulation on Various Effector Organs

Effector Organ	Sympathetic Effect	Parasympathetic Effect
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Conduction	Increased rate	Decreased rate
Strength	Increased	—
Blood Vessels	Mostly constriction; affects all organs	Dilation in a few organs (e.g., penis)
Lungs		
Bronchioles (tubes)	Dilation	Constriction
Mucous glands	Inhibition of secretion	Stimulation of secretion
Gastrointestinal Tract		
Motility	Inhibition of movement	Stimulation of movement

Figure 9.9a

e.g. smooth muscle of airways

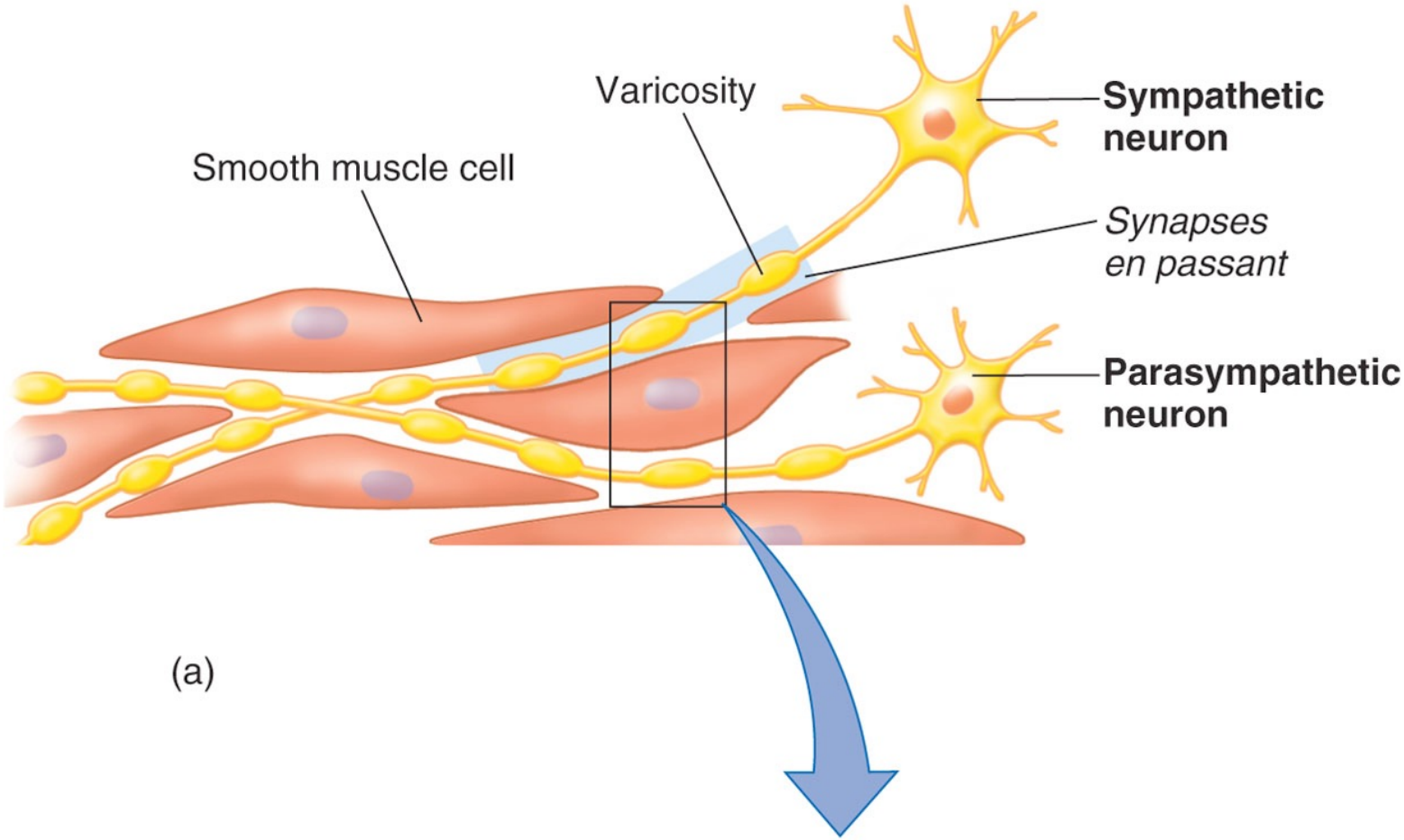
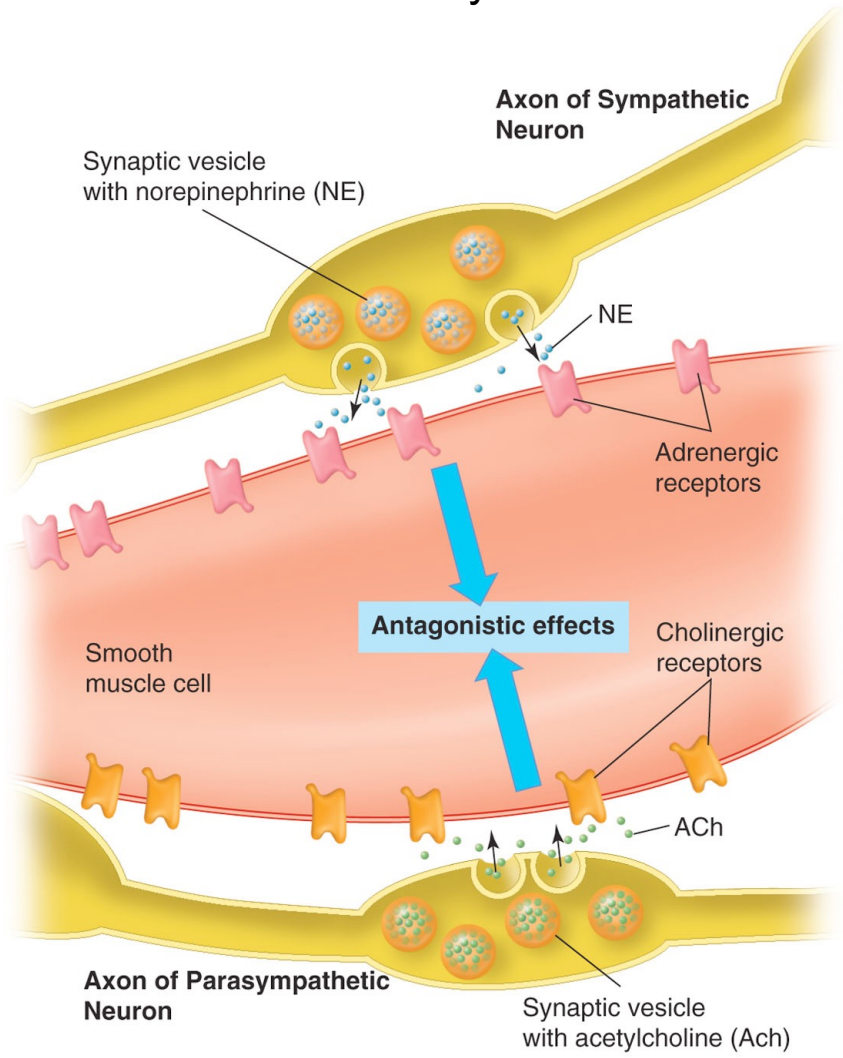


Figure 9.9b

e.g. smooth muscle of airways

sympathetic relaxation and **dilation** of airways

parasympathetic **constriction** of airways



(b)

Autonomic Nervous System Transmitters and Receptors

Acetylcholine -> Cholinergic Receptors

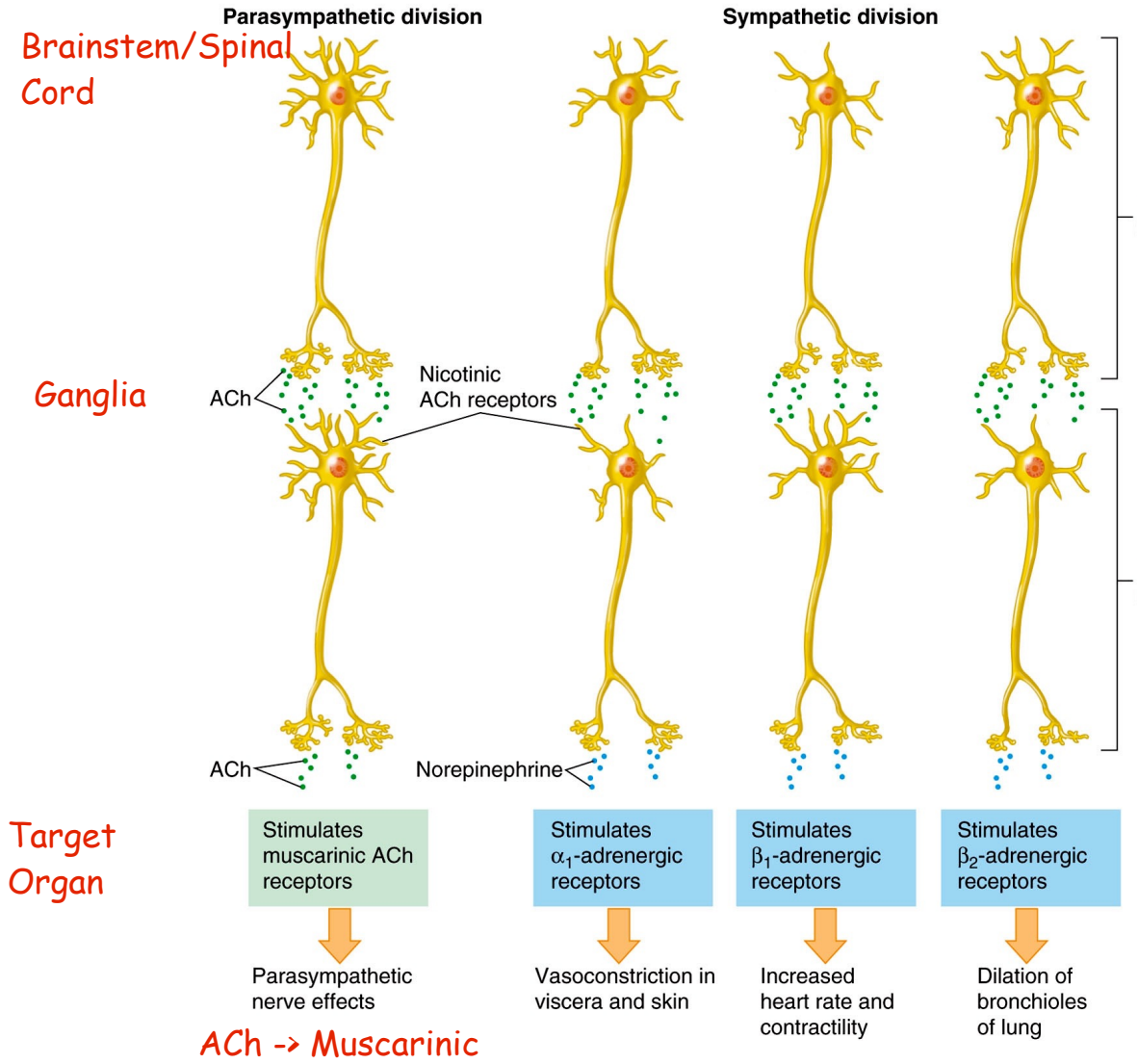
- Nicotinic (ligand gated Na+ channels)
- Muscarinic (G-protein-coupled receptors)

Norepinephrine -> Adrenergic Receptors

(Epinephrine from adrenal gland)

- alpha-adrenergic receptors (G-protein-coupled receptors)
- beta-adrenergic receptors (G-protein-coupled receptors)

Figure 9.10


Parasympathetic division
Sympathetic division
Brainstem/Spinal Cord
Ganglia
Target Organ
Preganglionic neurons
Postganglionic neurons
ACh
Nicotinic ACh receptors
ACh
Norepinephrine
Stimulates muscarinic ACh receptors
Stimulates α_1-adrenergic receptors
Stimulates β_1-adrenergic receptors
Stimulates β_2-adrenergic receptors
Parasympathetic nerve effects
Vasoconstriction in viscera and skin
Increased heart rate and contractility
Dilation of bronchioles of lung
ACh -> Nicotinic Receptors
NorEpi -> α or β
ACh -> Muscarinic

Terminology:

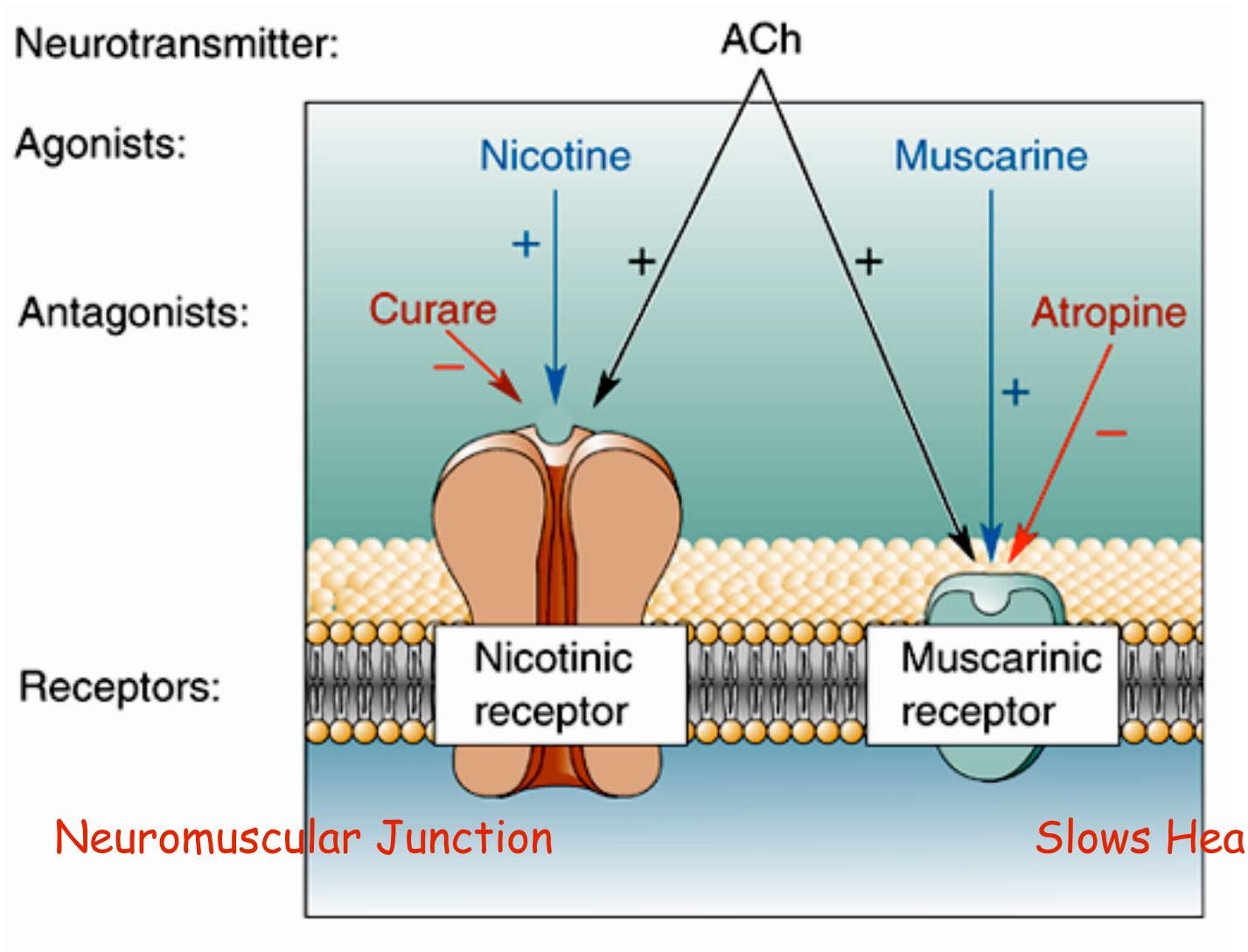
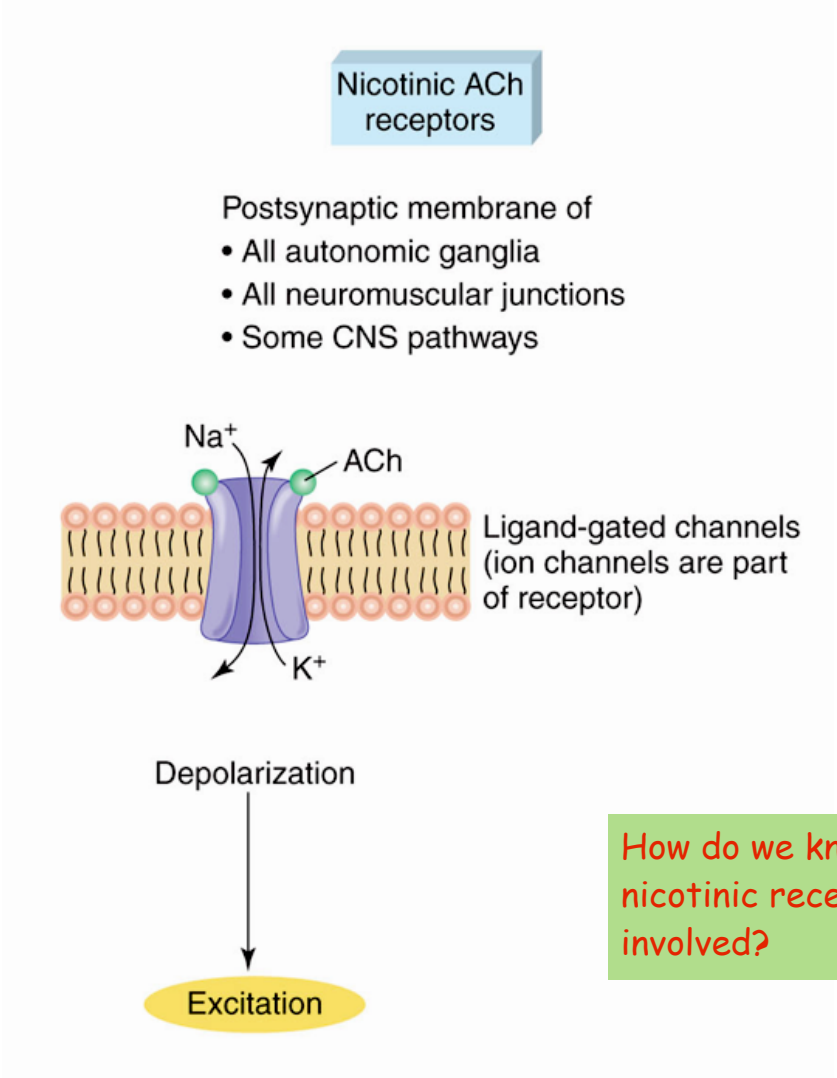


Figure 9.11



How do we know nicotinic receptors are involved?

Figu

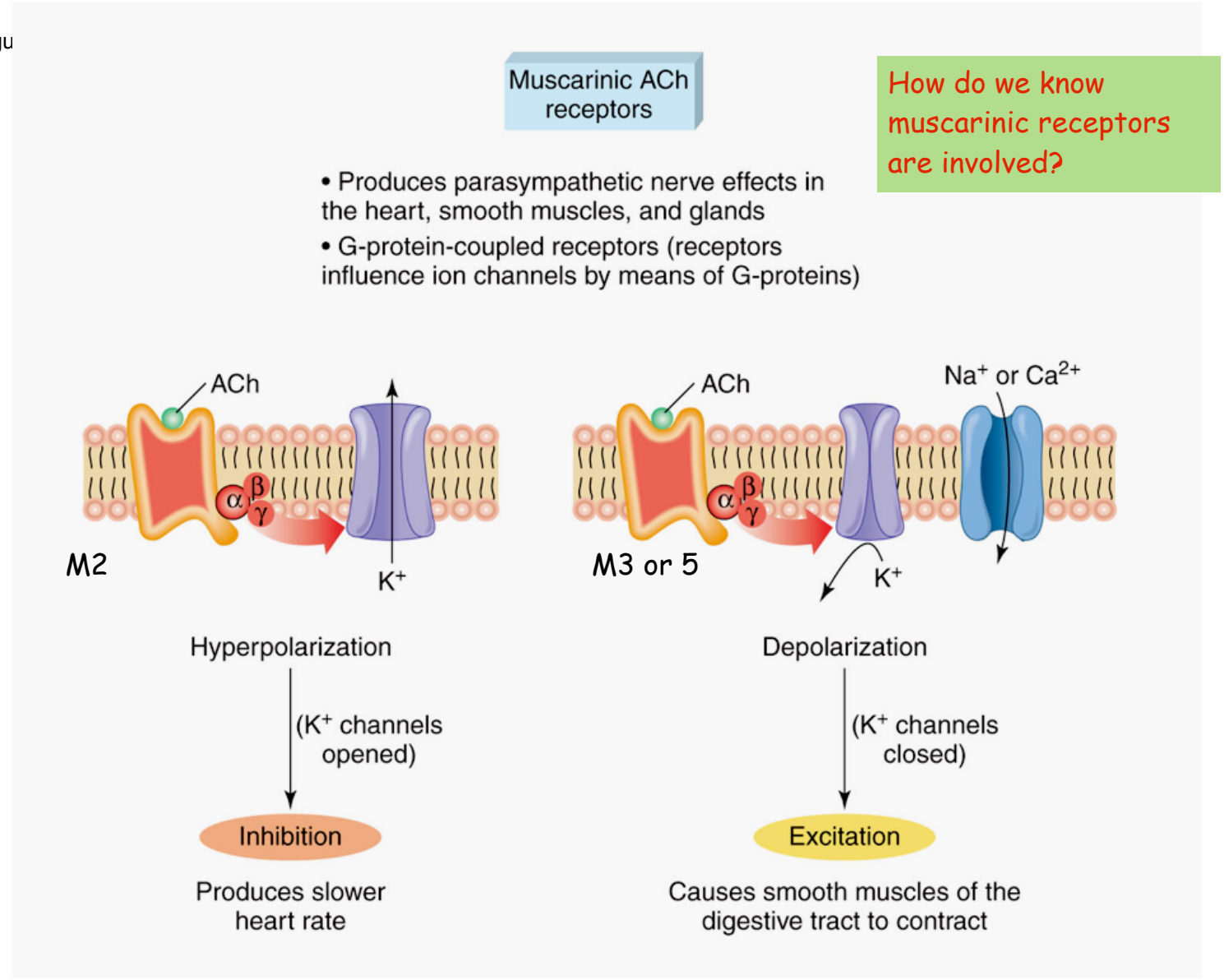

Muscarinic ACh receptors
• Produces parasympathetic nerve effects in the heart, smooth muscles, and glands
• G-protein-coupled receptors (receptors influence ion channels by means of G-proteins)
How do we know muscarinic receptors are involved?
ACh
α
β
γ
M2
K+
Hyperpolarization
(K+ channels opened)
Inhibition
Produces slower heart rate
ACh
Na+ or Ca2+
α
β
γ
M3 or 5
K+
Depolarization
(K+ channels closed)
Excitation
Causes smooth muscles of the digestive tract to contract

Table 9.6

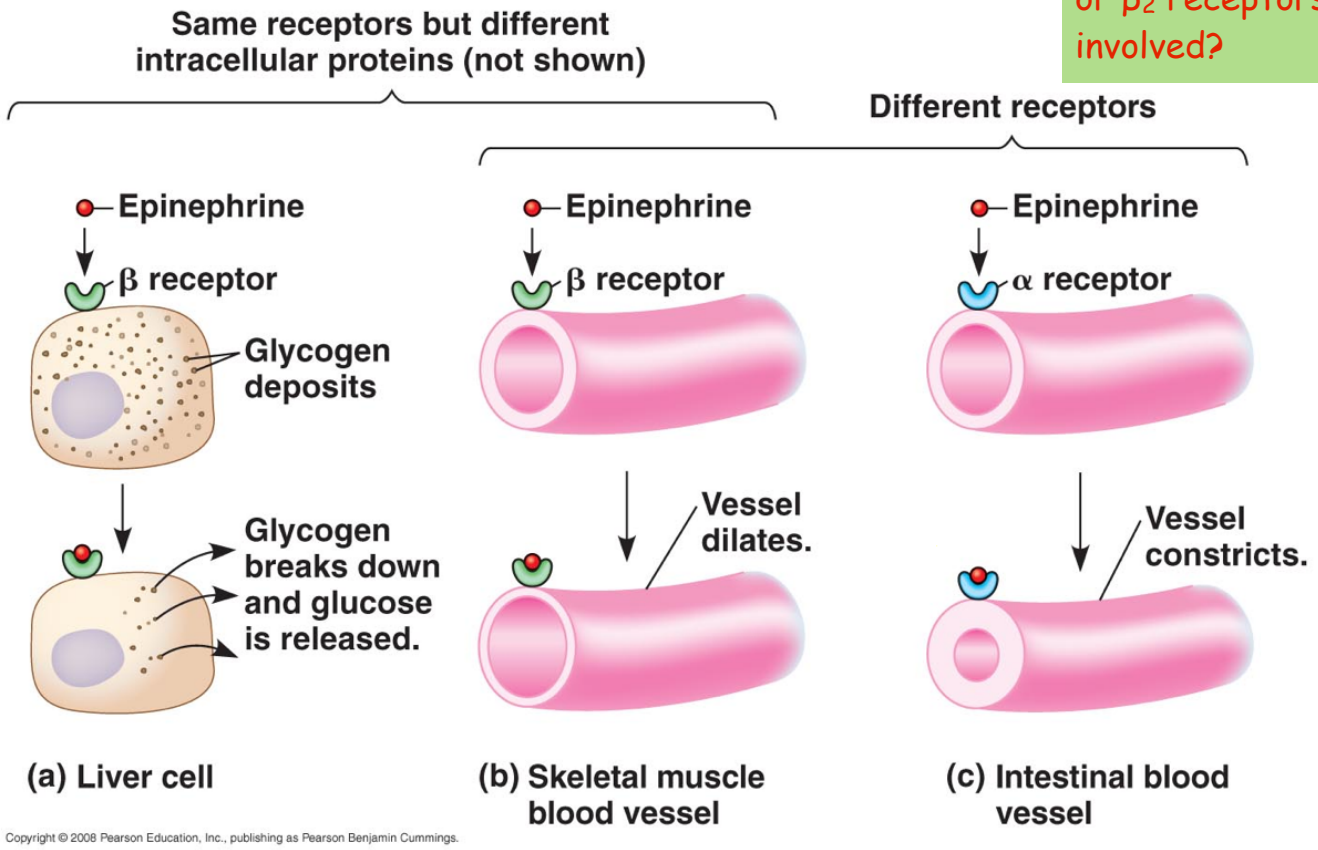
Table 9.6 | Cholinergic Receptors and Responses to Acetylcholine

Receptor	Tissue	Response	Mechanisms
Nicotinic	Skeletal muscle	Depolarization, producing action potentials and muscle contraction	ACh opens cation channel in receptor
Nicotinic	Autonomic ganglia	Depolarization, causing activation of postganglionic neurons	ACh opens cation channel in receptor
Muscarinic (M_3, M_5)	Smooth muscle, glands	Depolarization and contraction of smooth muscle, secretion of glands	ACh activates G-protein coupled receptor, opening Ca^{2+} channels and increasing cytosolic Ca^{2+}
Muscarinic (M_2)	Heart	Hyperpolarization, slowing rate of spontaneous depolarization	ACh activates G-protein coupled receptor, opening channels for K^+

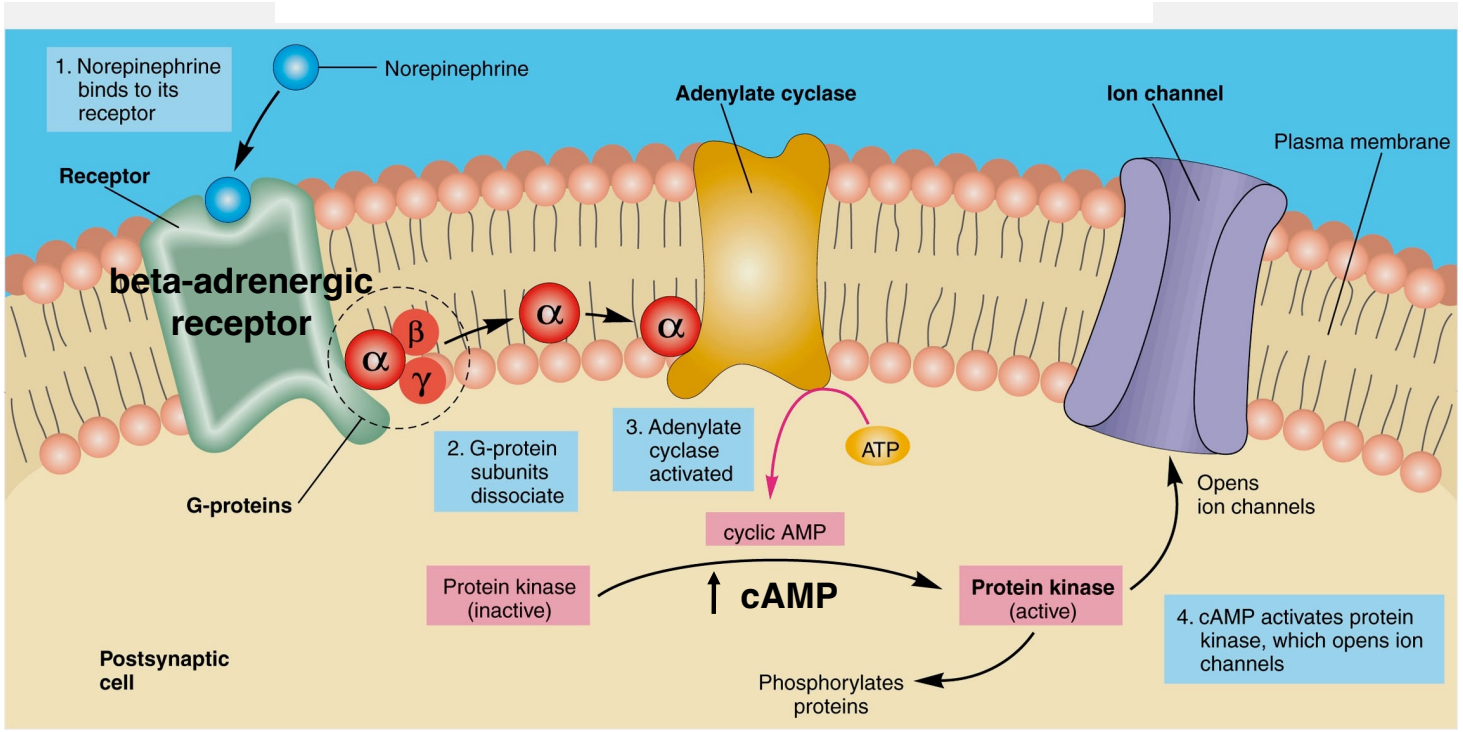
Source: Simplified from table 6-2, p. 119 of Goodman and Gilman's *The Pharmacological Basis of Therapeutics.* Ninth edition. J.E. Hardman et al., eds. 1996 and table 6-3, p. 156 of the Eleventh edition, 2006. McGraw-Hill.

Epinephrine (Adrenalin) secreted from Adrenal Gland & Autonomic Neurons during stress (one NT -> multiple effects)

How do we know α or β_1 or β_2 receptors are involved?



G-Proteins can affect second messenger signaling (e.g. cAMP levels in the cytoplasm)



Fox Figure 7.31

Table 9.5

beta$_1$ beta$_2$

Table 9.5 | Selected Adrenergic Effects in Different Organs

Organ	Adrenergic Effects of Sympathoadrenal System	Adrenergic Receptor
Eye	Contraction of radial fibers of the iris dilates the pupils	alpha$_1$
Heart	Increase in heart rate and contraction strength	beta$_1$
Skin and visceral vessels	Arterioles constrict due to smooth muscle contraction	alpha$_1$
Skeletal muscle vessels	Arterioles constrict due to sympathetic nerve activity	alpha$_1$
	Arterioles dilate due to hormone epinephrine	beta$_2$
Lungs	Bronchioles (airways) dilate due to smooth muscle relaxation	beta$_2$
Stomach and intestine	Contraction of sphincters slows passage of food	alpha$_1$
Liver	Glycogenolysis and secretion of glucose	alpha$_1$ beta$_2$

Source: Simplified from table 6-1, pp. 110–111, of Goodman and Gilman's *The Pharmacological Basis of Therapeutics.* Ninth edition. J.E. Hardman et al., eds. 1996. McGraw-Hill.

Table 9.7 | Adrenergic and Cholinergic Effects of Sympathetic and Parasympathetic Nerves

	Effect of			
	Sympathetic		Parasympathetic	
Organ	**Action**	**Receptor***	**Action**	**Receptor***
Eye				
Iris				
Radial muscle	Contracts	α_1	—	—
Circular muscle	—	—	Contracts	M
Heart				
Sinoatrial node	Accelerates	β_1	Decelerates	M
Contractility	Increases	β_1	Decreases (atria)	M

Table 9.7 | Adrenergic and Cholinergic Effects of Sympathetic and Parasympathetic Nerves

Organ	Effect of			
	Sympathetic		Parasympathetic	
	Action	Receptor*	Action	Receptor*
Vascular Smooth Muscle				
Skin, splanchnic vessels	Contracts	α,β	—	—
Skeletal muscle vessels	Relaxes	β_2	—	—
	Relaxes	M**	—	—
Bronchiolar Smooth Muscle	Relaxes	β_2	Contracts	M
Gastrointestinal Tract				
Smooth muscle				
Walls	Relaxes	β_2	Contracts	M
Sphincters	Constricts	α_1	Relaxes	M
Secretion	Decreases	α_1	Increases	M
Myenteric plexus	Inhibits	α_1	—	—

Be able to compare and contrast sympathetic and parasympathetic nervous system

Location of preganglion neurons

Location of ganglia

Neurotransmitters used by pre- and post ganglionic neurons

Role of sympathetic vs. parasympathetic system

Some examples of target organs:

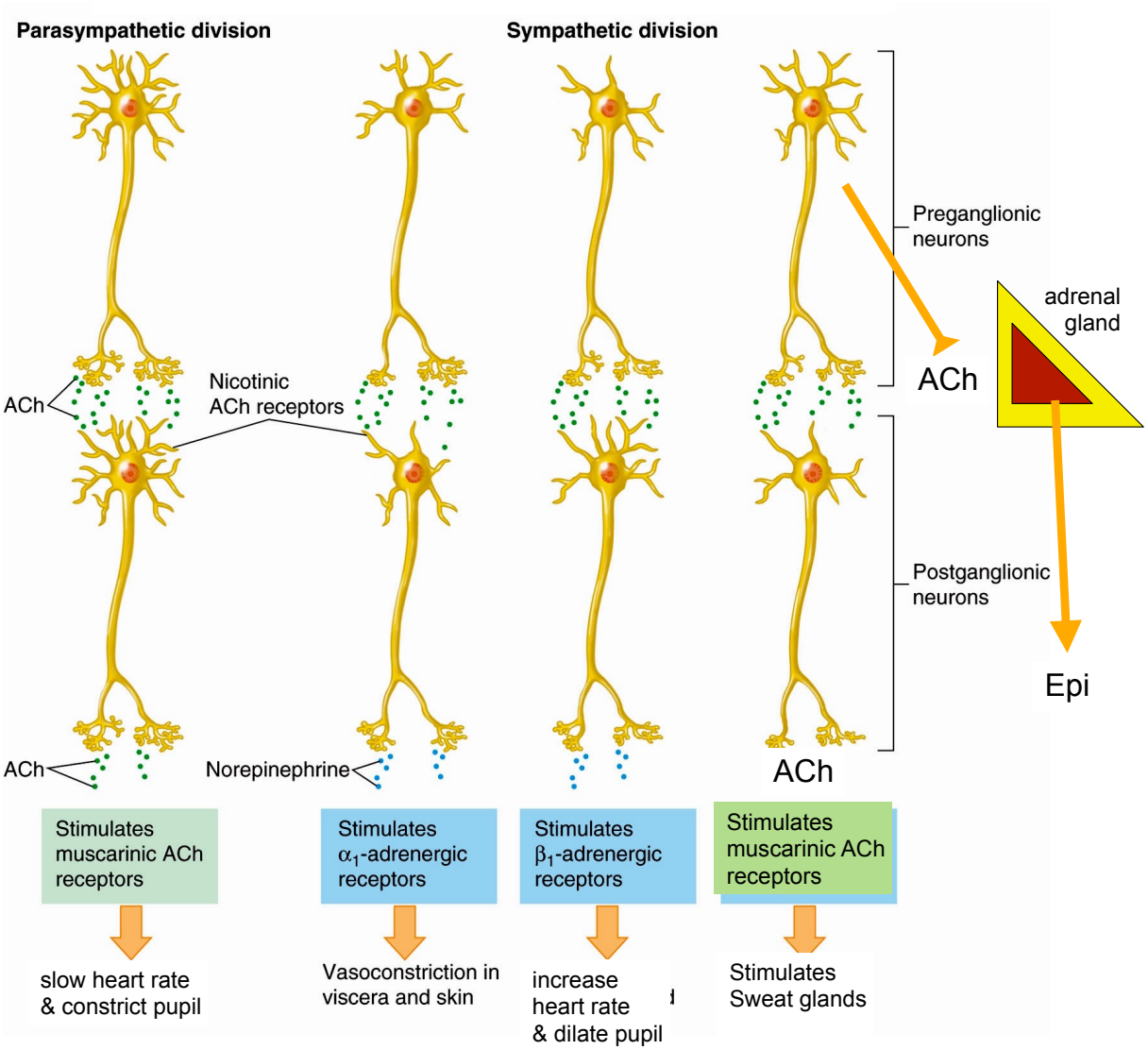
airways, pupil, sweating

Application	Effect of Vial 1	Effect of Vial 2
onto eye	no effect	Dilation of pupil
onto adrenal gland	epinephrine secretion	no effect
onto heart	no effect	speeds up heart
onto sweat gland	no effect	decreases sweating
into sympathetic chain ganglion	increased sympathetic response	no effect
into parasympathetic ganglion	increased parasympathetic response	no effect

You conclude that vial 1 or 2 contains:

a. acetylcholine
b. atropine
c. cocaine
d. epinephrine
e. nicotine

Figure 9.10



Pharmacology of Autonomic Nervous System

Application	Effect of Vial 1
onto eye — muscarinic ACh (constriction) vs. beta-adrenergic receptors (dilation)	no effect
onto adrenal gland — nicotinic ACh receptors	epinephrine secretion
onto heart — muscarinic ACh (slow) vs. beta-adrenergic receptors (speed up)	no effect
onto sweat gland — muscarinic ACh receptors	no effect
into sympathetic chain ganglion — nicotinic ACh receptors	increased sympathetic response
into parasympathetic ganglion — nicotinic ACh receptors	increased parasympathetic response

1. You conclude that vial 1 contains:
   a. acetylcholine → muscarinic & nicotinic ACh receptors
   b. atropine → block muscarinic ACh receptors
   c. cocaine → enhance adrenergic receptors
   d. epinephrine → adrenergic receptors
   e. nicotine → nicotinic ACh receptors

Application	Effect of Vial 2
onto eye muscarinic ACh (constriction) vs. beta-adrenergic receptors (dilation)	Dilation of pupil
onto adrenal gland nicotinic ACh receptors	no effect
onto heart muscarinic ACh (slow) vs. beta-adrenergic receptors (speed up)	speeds up heart
onto sweat gland muscarinic ACh receptors	decreases sweating
into sympathetic chain ganglion nicotinic ACh receptors	no effect
into parasympathetic ganglion nicotinic ACh receptors	no effect

2. You conclude that vial 2 contains:

a. acetylcholine → muscarinic & nicotinic ACh receptors
b. atropine → block muscarinic ACh receptors
c. cocaine → ~~enhance adrenergic receptors~~
d. epinephrine → adrenergic receptors
e. nicotine → nicotinic ACh receptors

Human Phys PCB4701

Autonomic Nervous System: Examples & Disorders
Fox Chapter 9 part 2

Examples of Autonomic Nervous System

- Pupil dilation & contraction
- Sweating
- Horner's Syndrome
- Organophosphate Poisoning

Central Regulation of Autonomic Nervous System

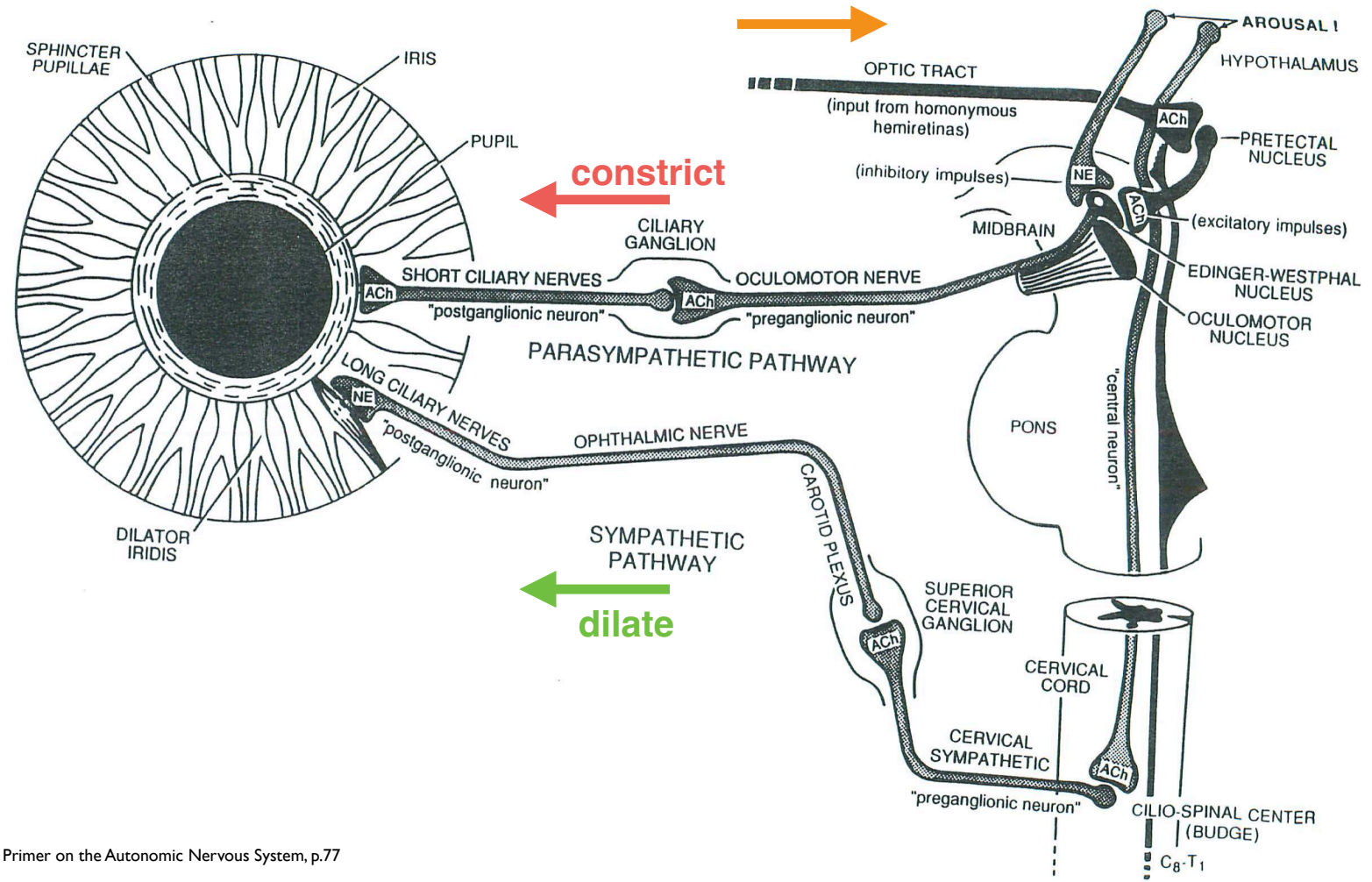
- brainstem
- hypothalamus
- *example: Thermoregulation & Fever*

Pupil Dilation & Constriction
Light via optic nerve (II) stimulates parasympathetic nerve (III) to constrict pupillary sphincter muscle (ACh muscarinic receptors)
Blocked by atropine -> pupil dilation
Sympathetic nerves cause dilation of pupil by stimulating pupillary dilator muscle (NE beta-adrenergic receptors)
Cocaine -> enhanced NE levels -> enhanced dilation

Hidrosis (sweating)
Sympathetic postganglionic neurons synapse onto sweat glands in the skin
Sympathetic neurons release **ACh** (**not NE**) to stimulate sweating
Hyperhidrosis - excessive sweating -- treated with anticholinergics, botulin toxin (botox) that blocks ACh release, or **sympathectomy** (cutting sympathetic nerves)

Horner's Syndrome
Damage to sympathetic nerves on one side of neck
Unilateral (one-sided) constriction of pupil, anhydrosis (lack of sweat), flushing

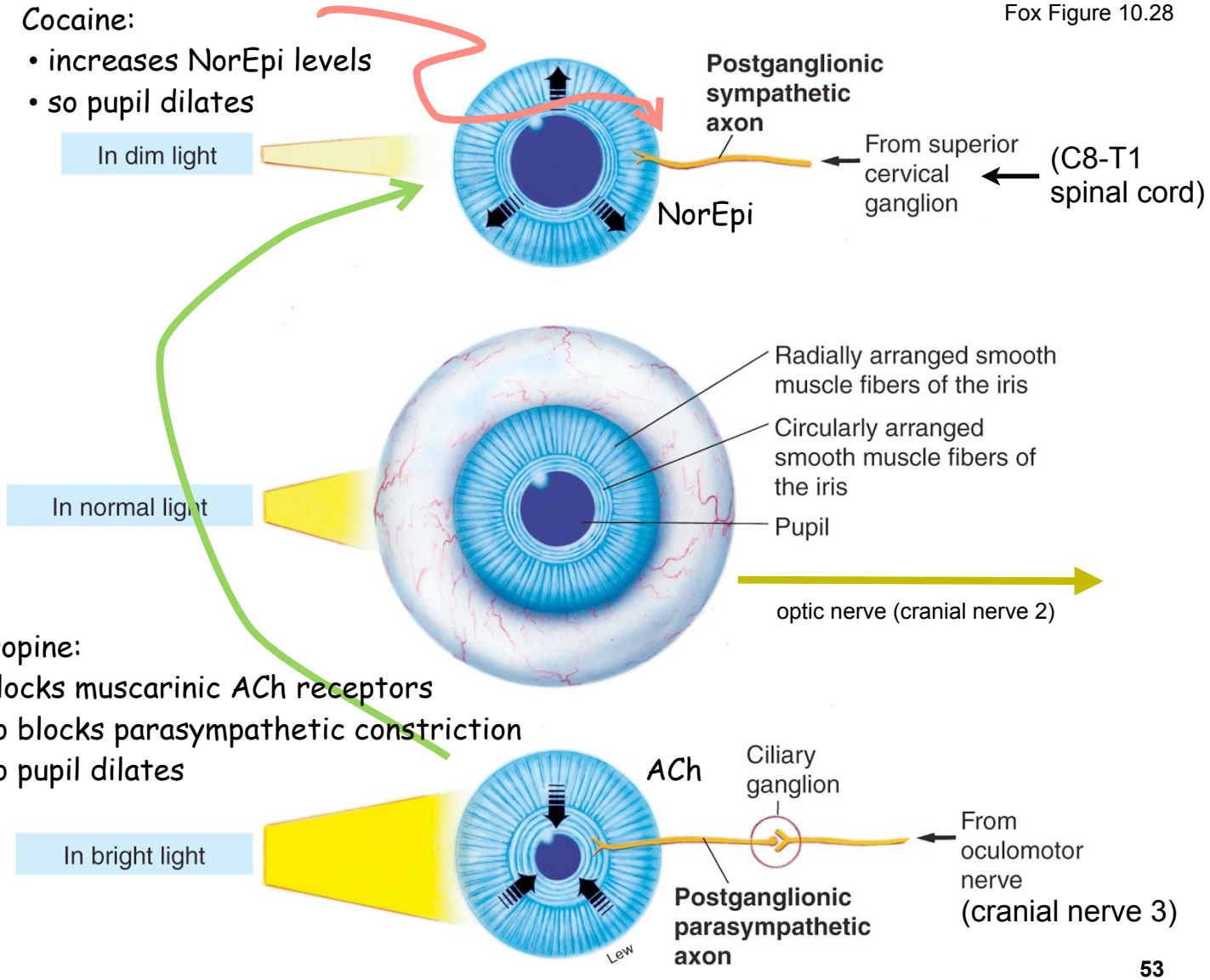
Organophosphates
insecticides that block cholinesterase enzyme -> enhanced ACh neurotransmission at all synapses
Treated with atropine to block effects of elevated ACh



Primer on the Autonomic Nervous System, p.77

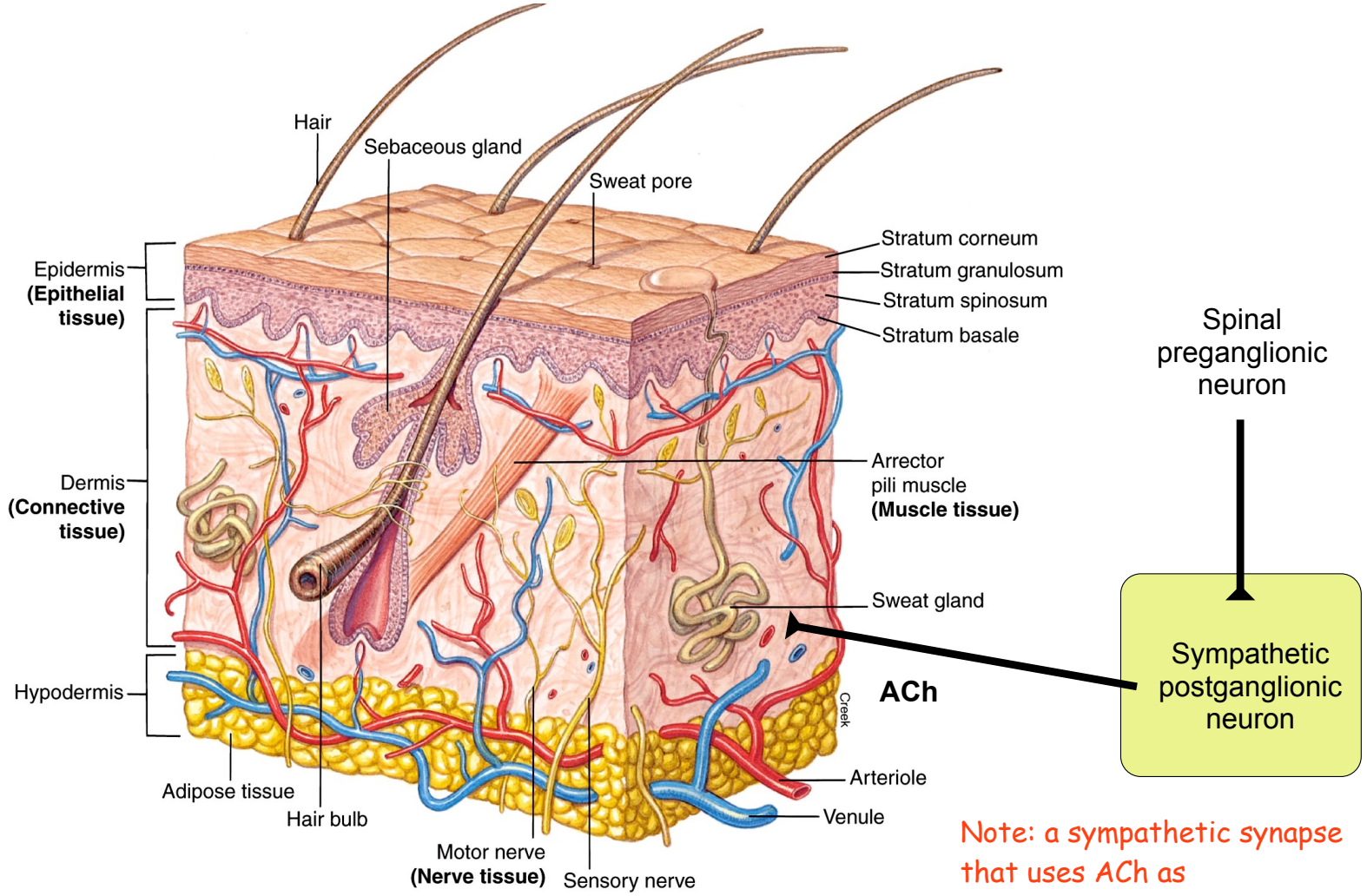
Fox Figure 10.28

Cocaine:
- increases NorEpi levels
- so pupil dilates

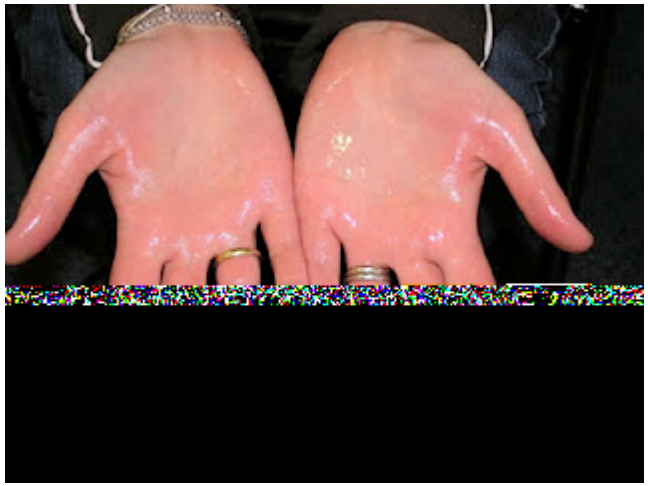


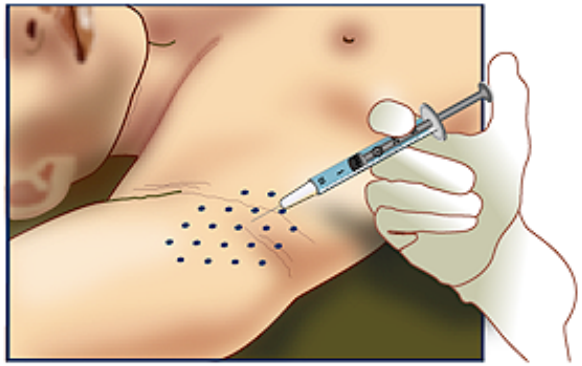
Atropine:
- blocks muscarinic ACh receptors
- so blocks parasympathetic constriction
- so pupil dilates

Figure 1.22


Hair
Sebaceous gland
Sweat pore
Epidermis
(Epithelial tissue)
Stratum corneum
Stratum granulosum
Stratum spinosum
Stratum basale
Dermis
(Connective tissue)
Arrector pili muscle
(Muscle tissue)
Sweat gland
Hypodermis
ACh
Creek
Arteriole
Venule
Adipose tissue
Hair bulb
Motor nerve
(Nerve tissue)
Sensory nerve
Spinal preganglionic neuron
Sympathetic postganglionic neuron
Note: a sympathetic synapse that uses ACh as transmitter

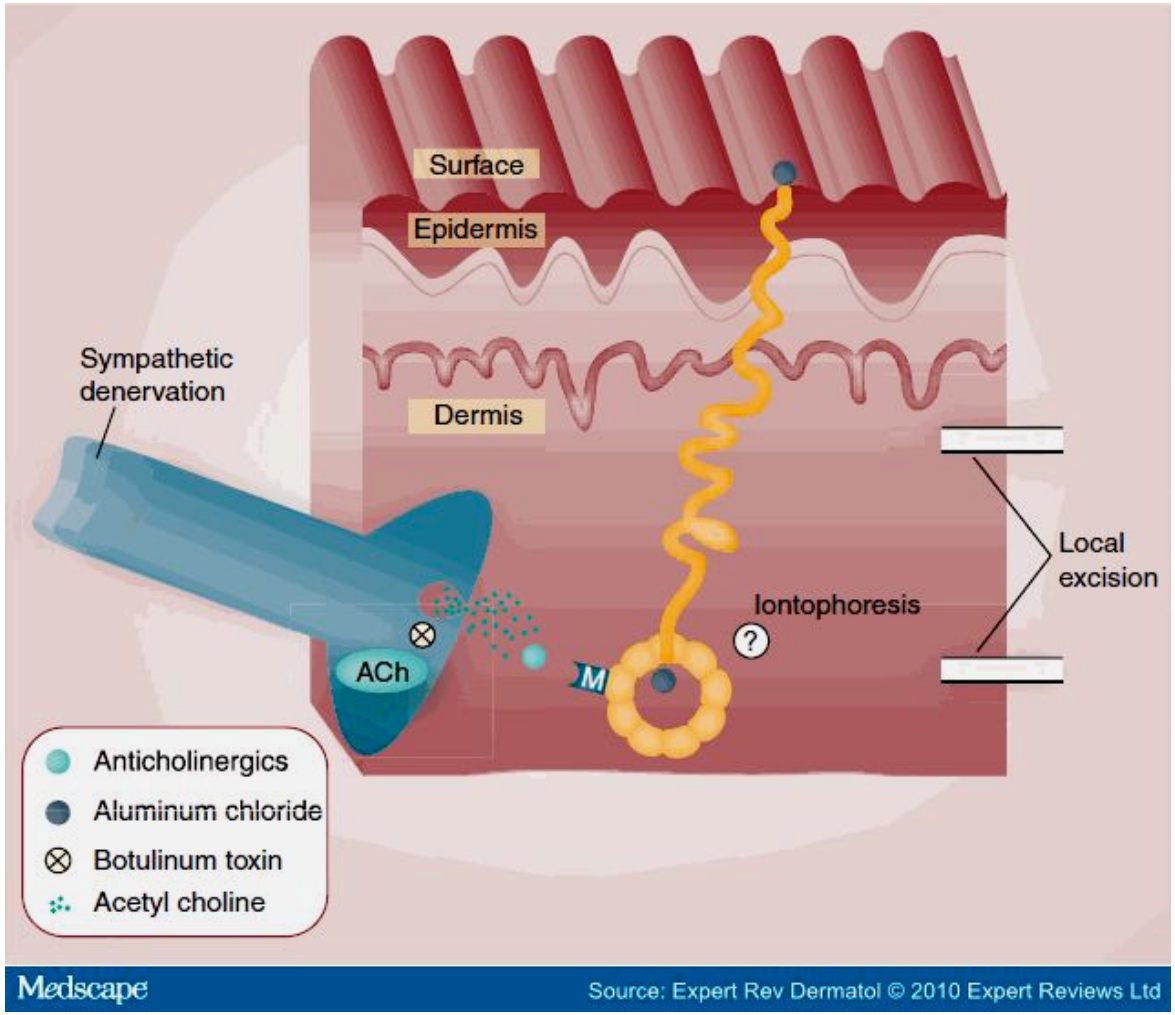
Hyperhidrosis - Excessive sweating





Botox injections

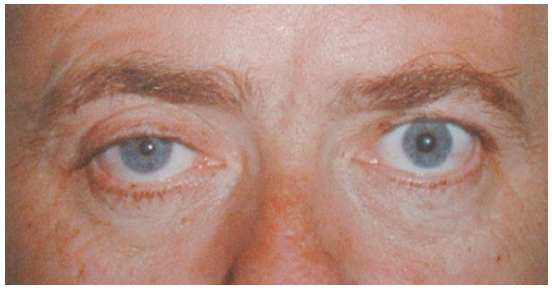
Sweating and Hyperhidrosis



Horner's Syndrome

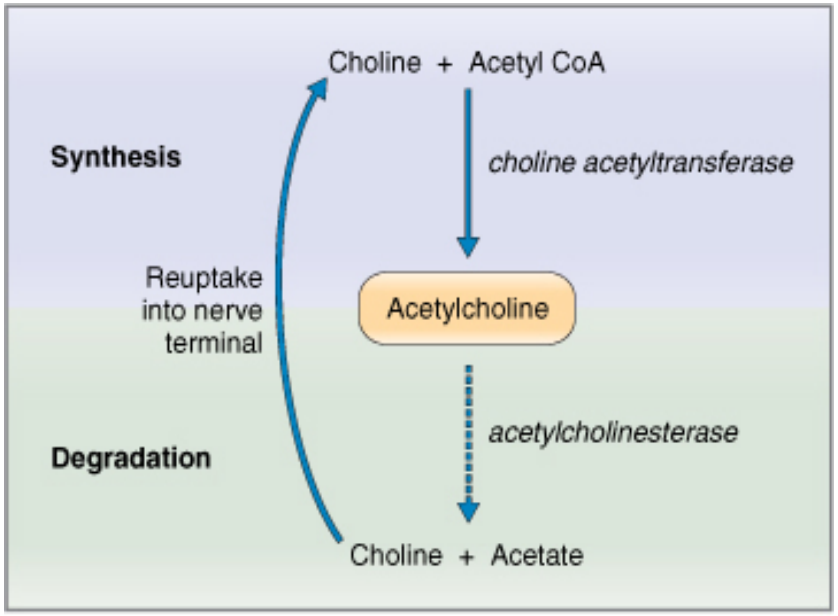
Loss of sympathetic innervation of the eye and face on one side (unilateral deficit)

1. Drooping eyelid (Ptosis)
2. Constricted pupil
3. Reduced sweating on the affected facial side



Horner' syndrome due to grenade wound of right side of neck (Bing's p. 102)

Organophosphates block degradation of ACh



Organophosphate pesticides (Malathion) and "nerve gas" (Sarin) are AchE inhibitors. Poisoning will present with symptoms of cholinergic activation.

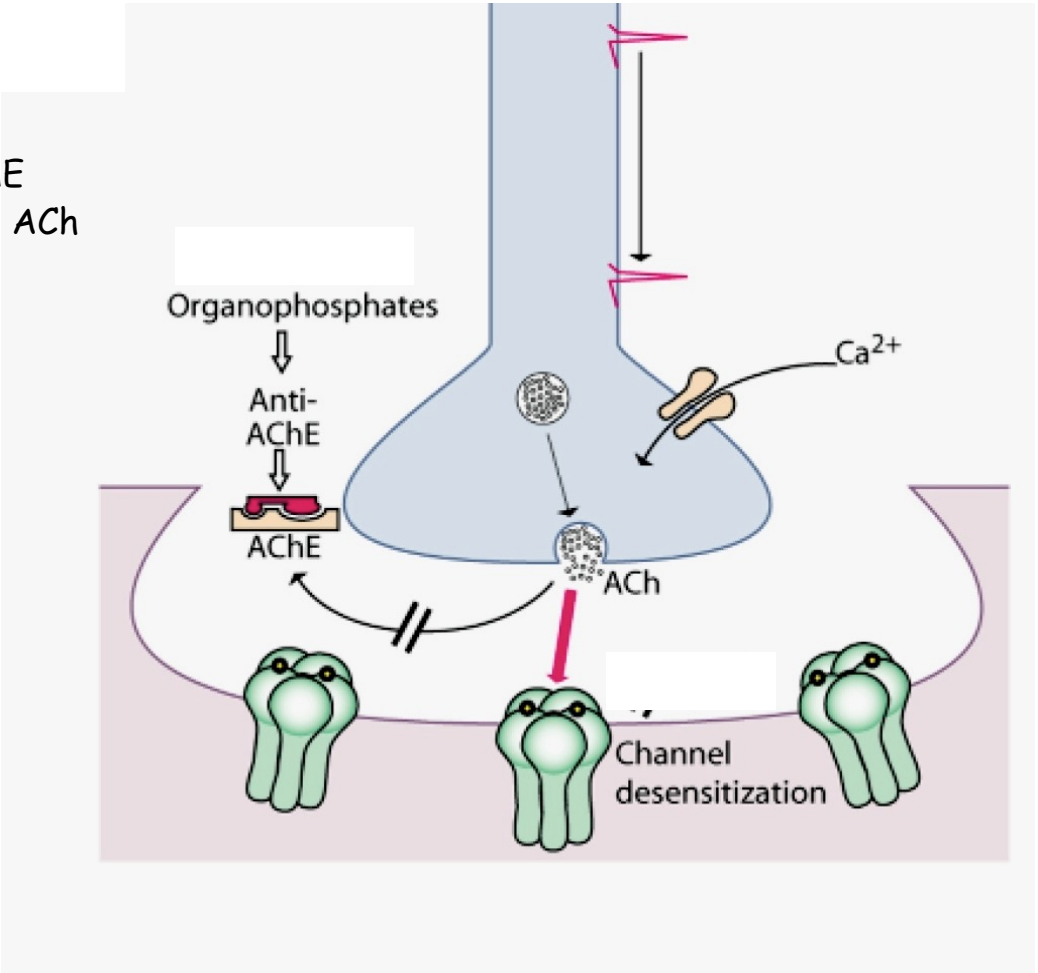
Activation of nicotinic ACh receptors on ganglionic synapses and neuromuscular junction.

Activation of muscarinic ACh receptors at parasympathetic target synapse

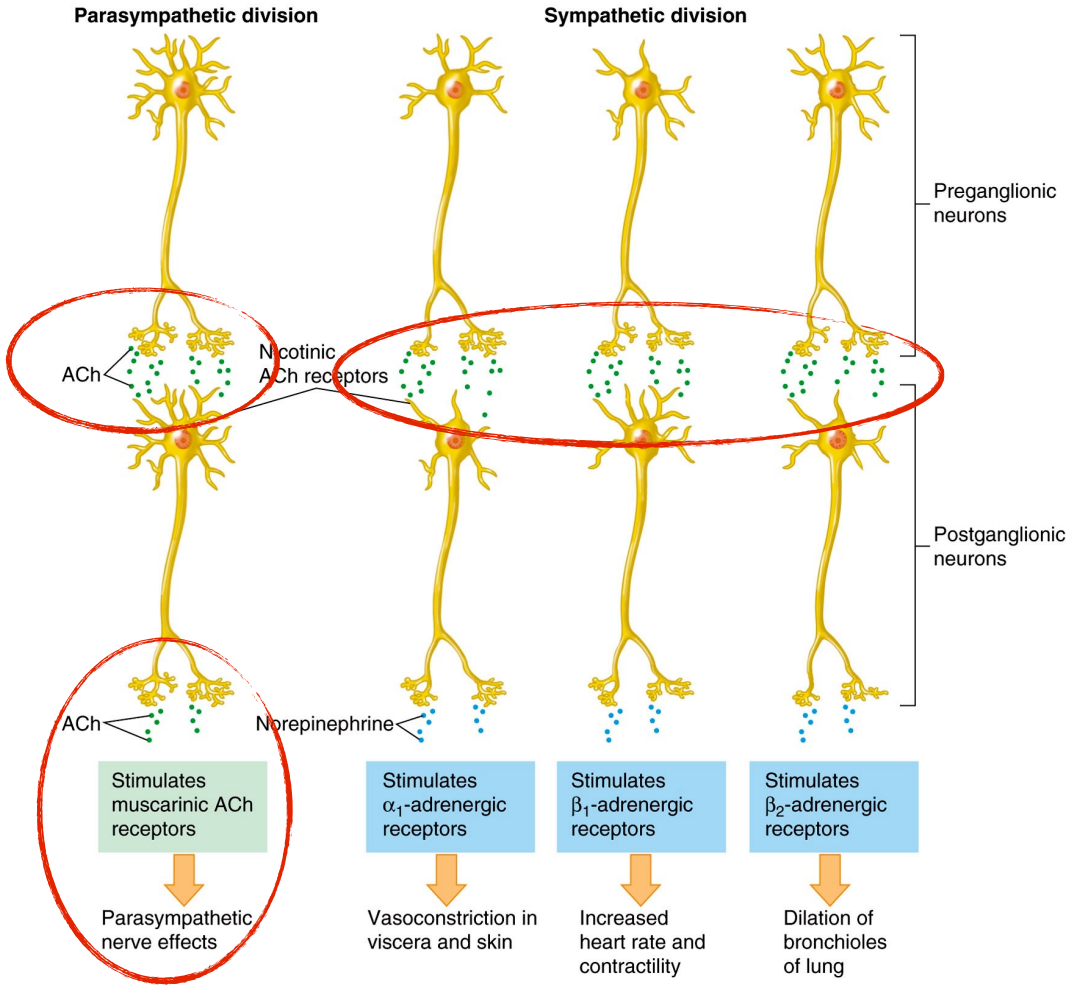
(and activation of sweat glands at cholinergic sympathetic synapse).

Organophosphates are powerful (long-lasting) AChE inhibitors used as pesticides

inhibition of AChE causes increased ACh in cholinergic synapses, so bigger, longer response



AChE inhibitors boost ACh everywhere



Common Symptoms Associated with Organophosphate Pesticide Poisoning.

Degree of Poisoning	Symptoms
Mild	Fatigue, headache, dizziness, blurred vision, excessive sweating/salivation, nausea/vomiting, stomach cramps, and diarrhea.
Moderate	Inability to walk, weakness, chest discomfort, constriction of pupils, and mild symptoms that are more severe.
Severe	Unconsciousness, severe constriction of pupils, muscle twitching, running nose, drooling, breathing difficulty, coma, and death.

July 2013

By RYAN JASLOW / CBS NEWS / July 24, 2013, 5:05 PM

Organophosphate pesticides eyed as cause of India poisonings: How toxic?

Some states require employers to enroll their employees who handle such pesticides in a cholinesterase-monitoring program. Although Florida law does not require employers of pesticide handlers to monitor these employee's cholinesterase levels, some employers in Florida — including the University of Florida — voluntarily enroll their employees who handle pesticides in a cholinesterase-monitoring program.

The BBC quoted a police official last week who said, "It was the high quantity of monocrotophos insecticide found in the food which proved fatal for the schoolchildren." The incident has been blamed on a bottle of pesticide being used instead of cooking oil to cook the free school lunches of rice, lentils, soybeans and potatoes.

The affected children, who were between the ages of 5 and 12, got sick shortly after eating lunch Tuesday July 16 at the school in Gandamal village. School authorities stopped serving the meal once the children began vomiting. The school's principal, who went into hiding after the incident, was arrested Tuesday.

Treatment of organophosphate (OP) poisoning involves assisted ventilation, blocking muscarinic activation with atropine and attempting to reactivate AchE

1. Organophosphorus (OP) insecticide poisoning is a major global clinical problem, killing an estimated 200,000 people each year.

2. Restricting agricultural use of highly toxic OP insecticides will reduce regional suicide rates. However, current agricultural policies make it unlikely that they will soon be banned. Effective clinical therapies are required.

3. OP compounds inhibit acetylcholinesterase (AchE), resulting in overstimulation of cholinergic synapses. Patients die mostly from respiratory failure and lung injury, although there is variability in the clinical syndrome.

4. Treatment involves resuscitation, administration of the muscarinic antagonist **atropine** and an oxime **acetylcholinesterase reactivator** , such as pralidoxime, and assisted ventilation as necessary.

(Eddleston et al. PLoS Med 6(6): e1000104, 2009)