AUTONOMIC NERVOUS SYSTEM

University of Hawai‘i Hilo Pre-Nursing Program
NURS 203 – General Pharmacology
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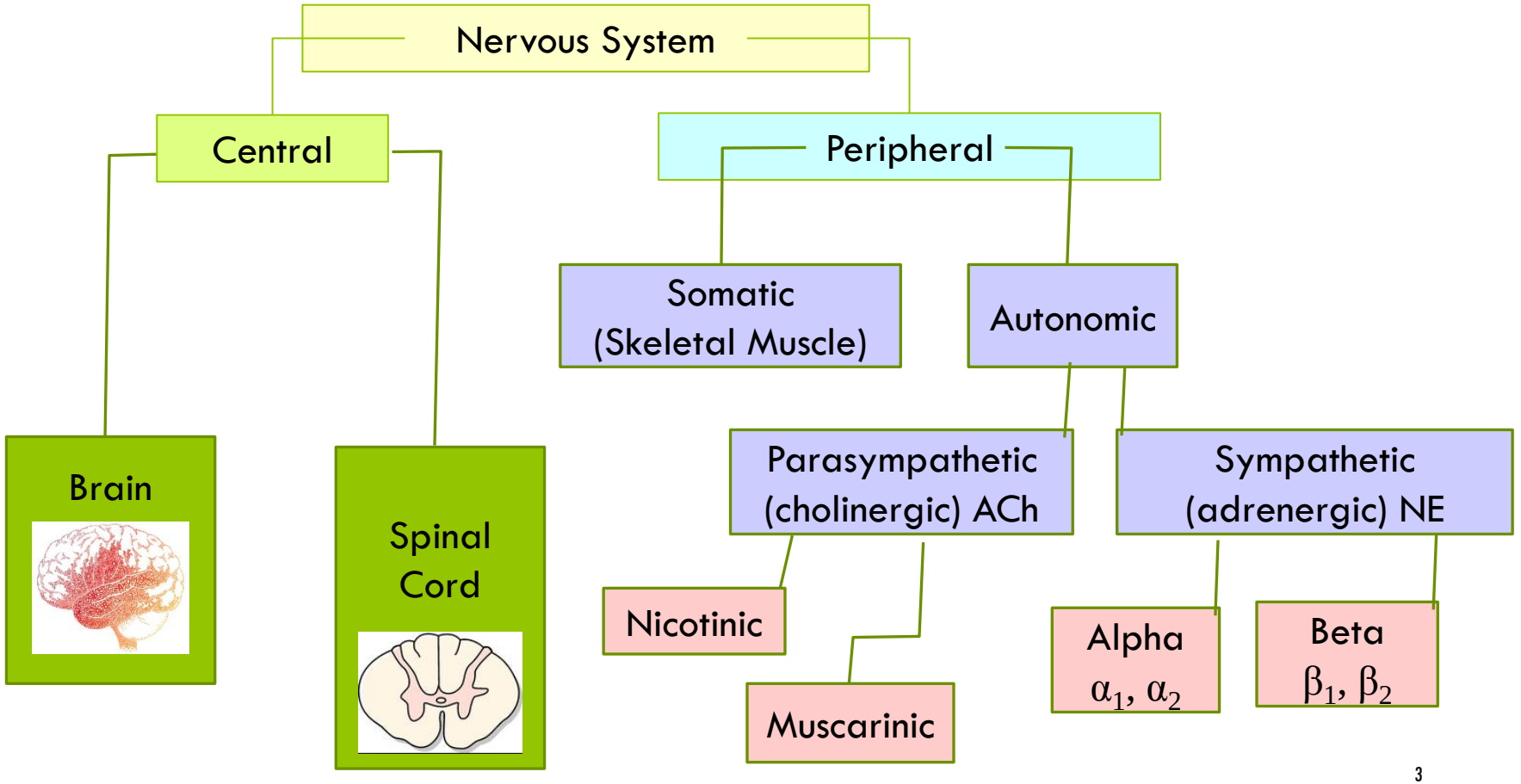
LEARNING OBJECTIVES

- Understand the basic function of the autonomic nervous system (ANS)
- Know the neurotransmitters and receptors of each branch of the autonomic nervous system
- Understand if a tissue or organ is being activated by a certain branch of the ANS what the resulting action would be
- Understand how these two systems work in concert for daily living and situation of fight or flight

AUTONOMIC NERVOUS SYSTEM – WHERE IT FITS IN



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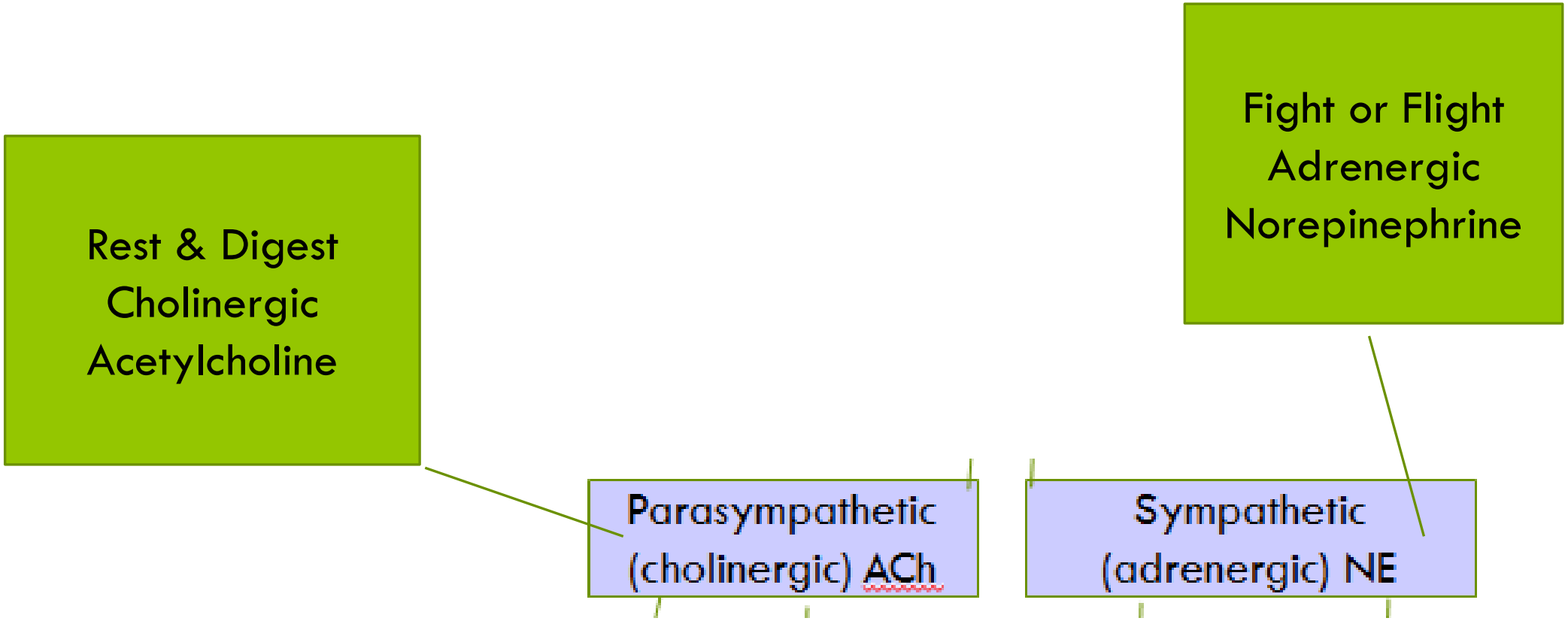

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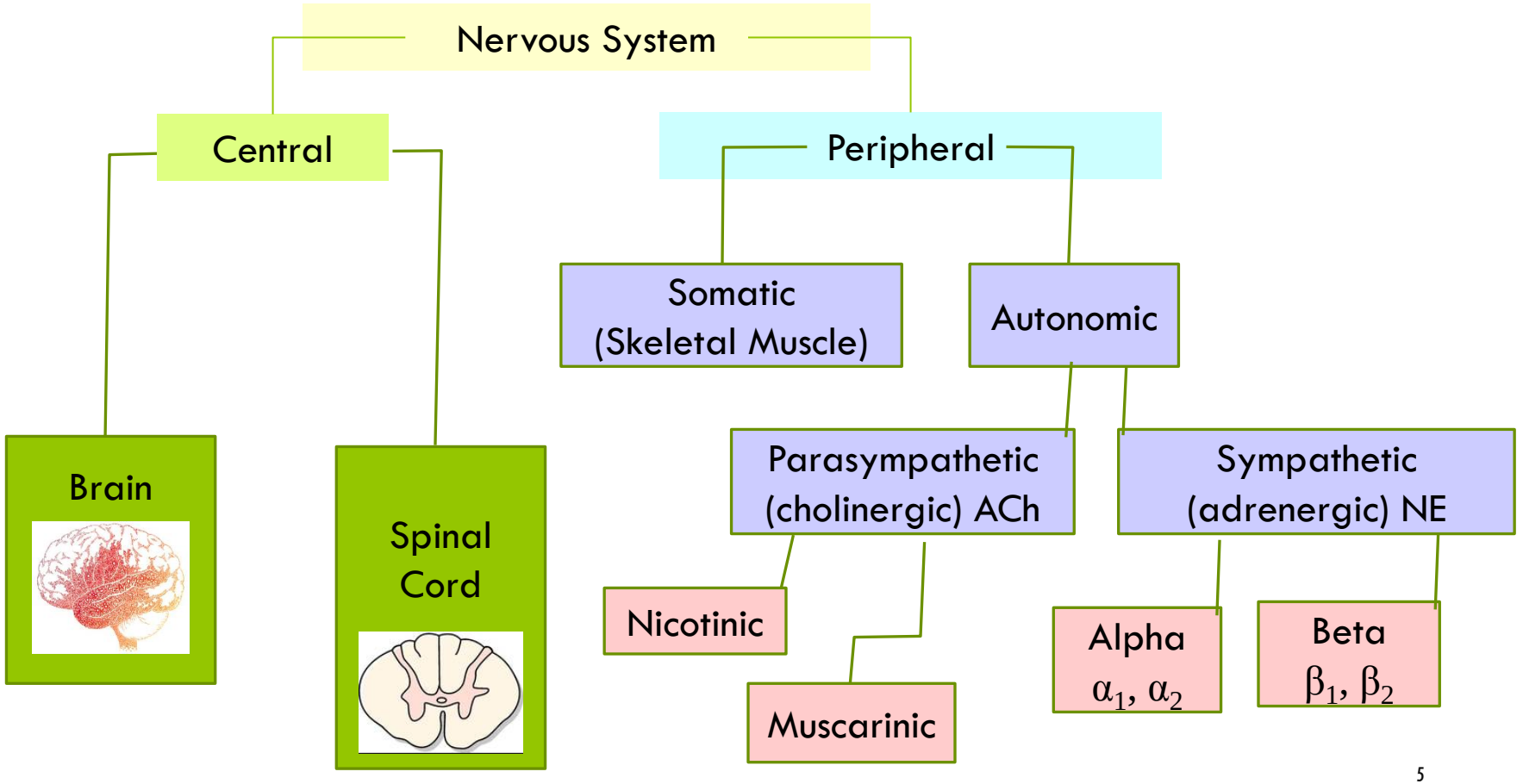
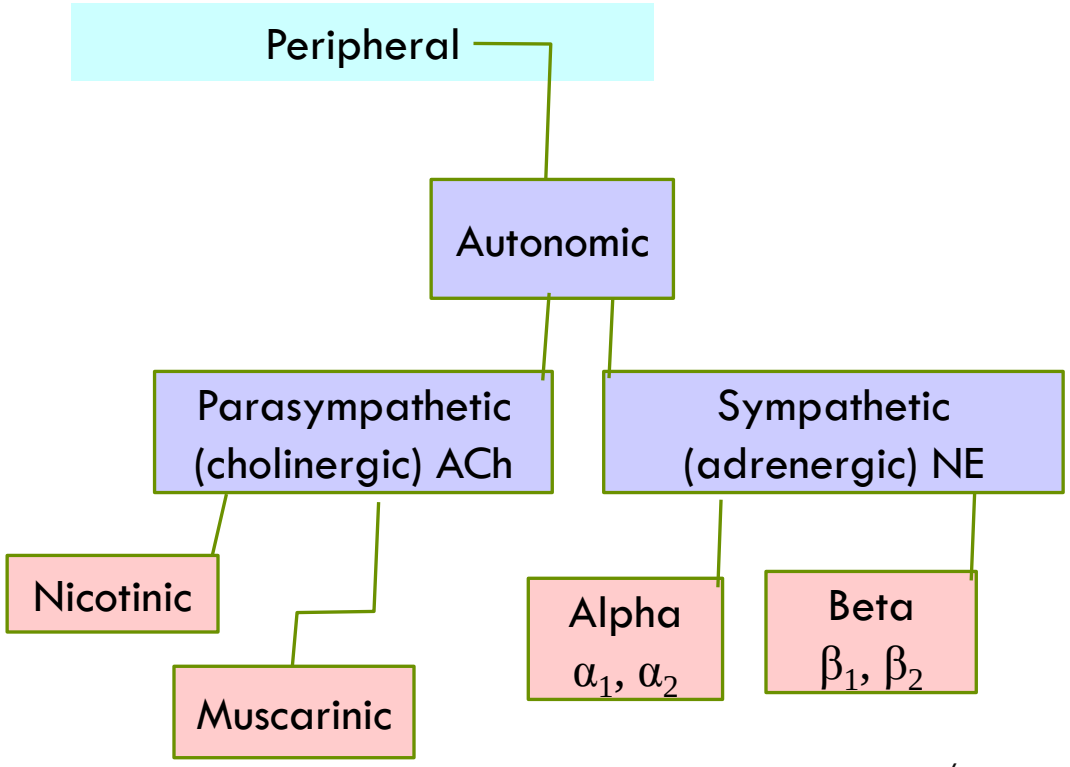
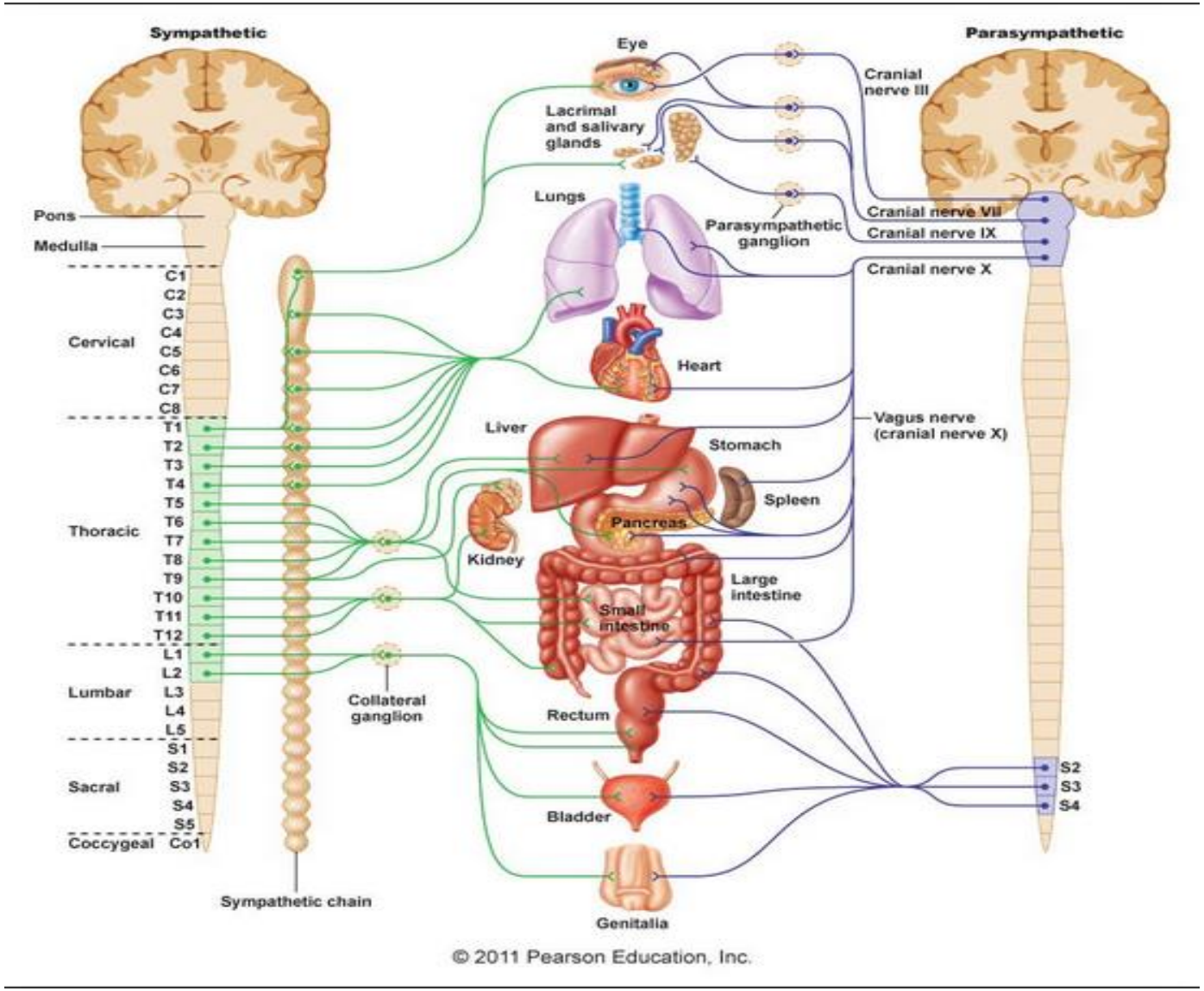


AUTONOMIC NERVOUS SYSTEM (ANS)

- Parasympathetic NS
  - Nicotinic
  - Muscarinic
- Sympathetic NS
  - Alpha
  - Beta
- Nerves
  - Carrying ACh
    - Cholinergic
  - Carrying NE
    - Adrenergic

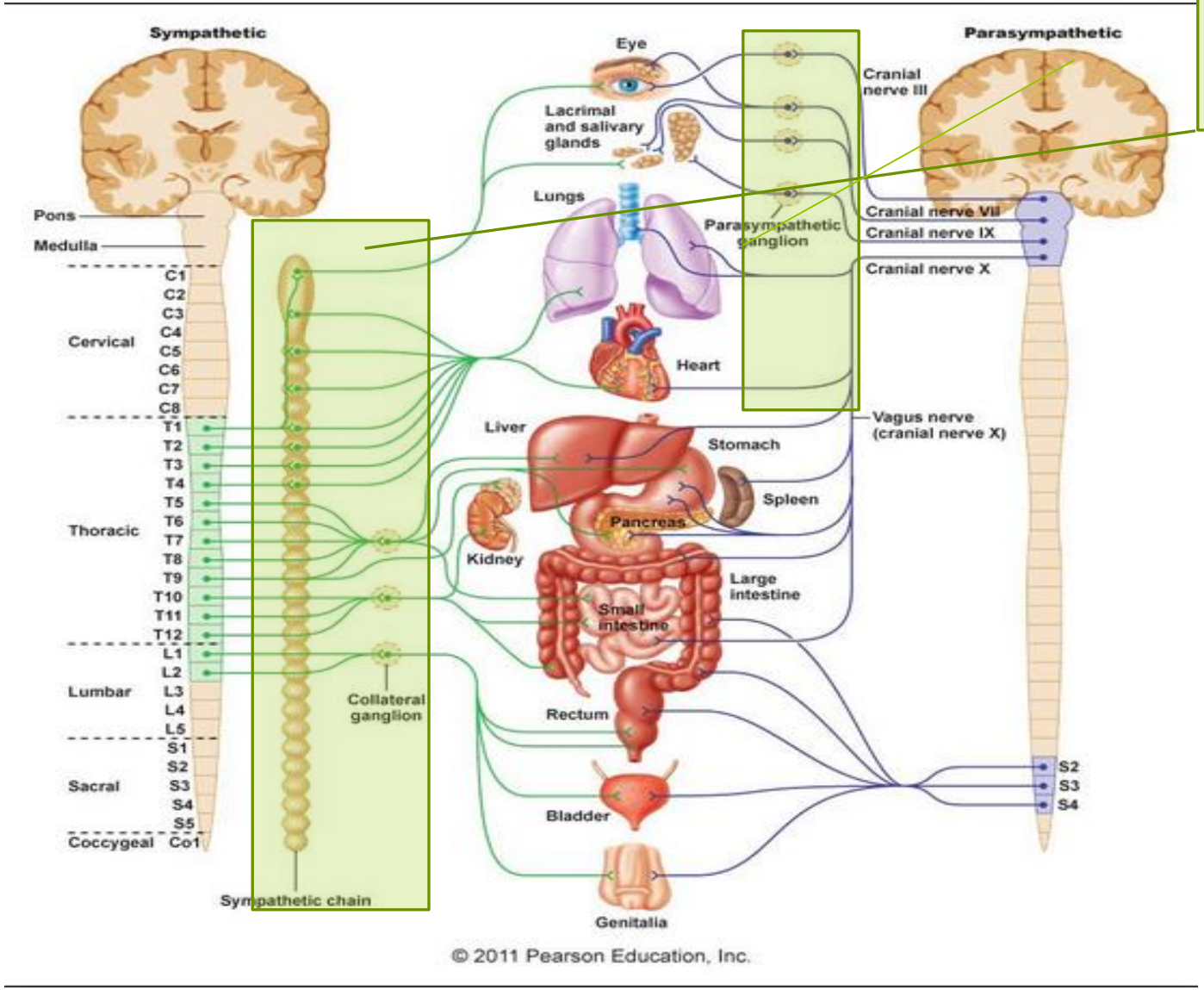


AUTONOMIC NERVOUS SYSTEM (ANS)



AUTONOMIC NERVOUS SYSTEM (ANS)

Ganglion: Group of nerve cell bodies. Connects pre and post ganglionic nerves.



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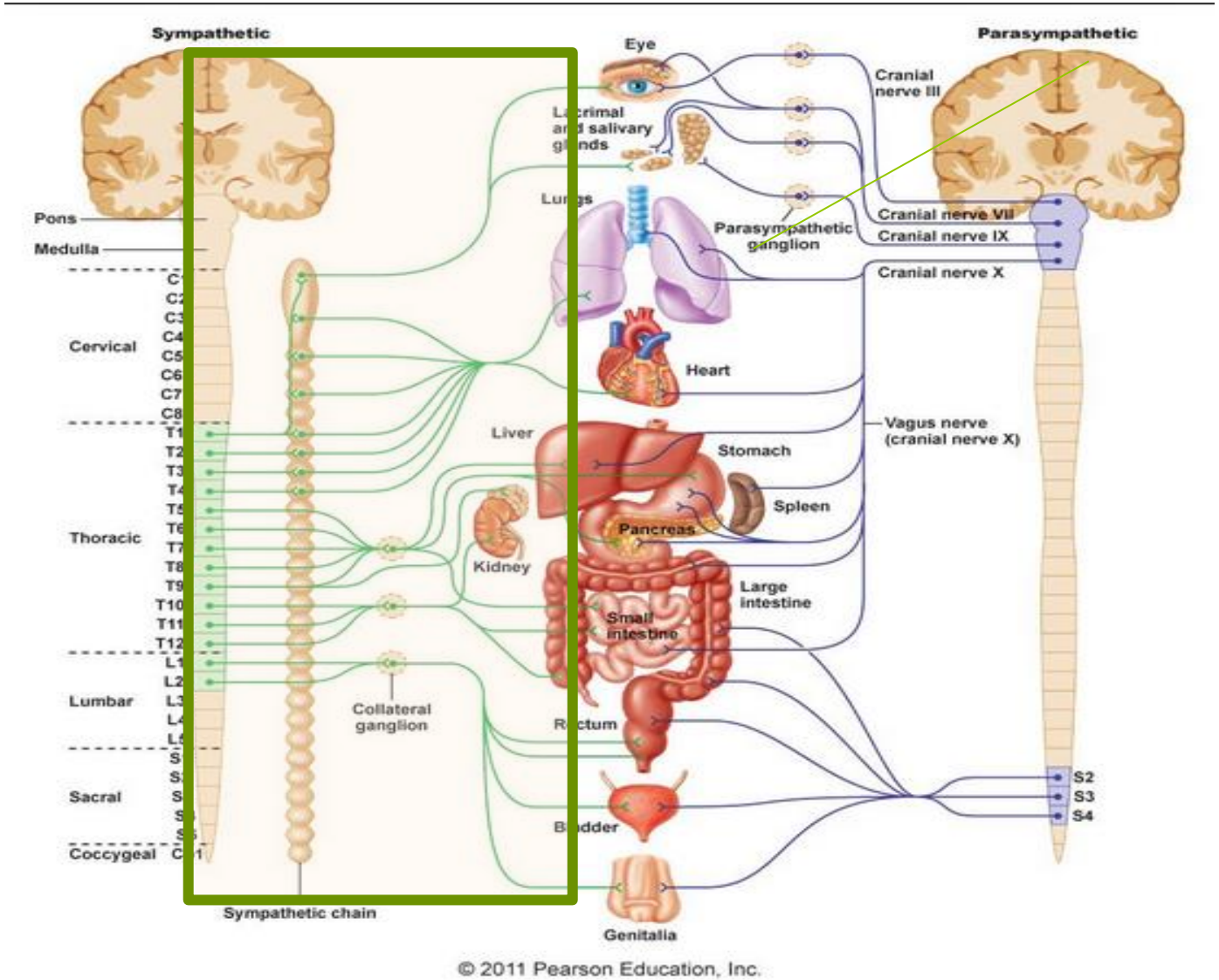

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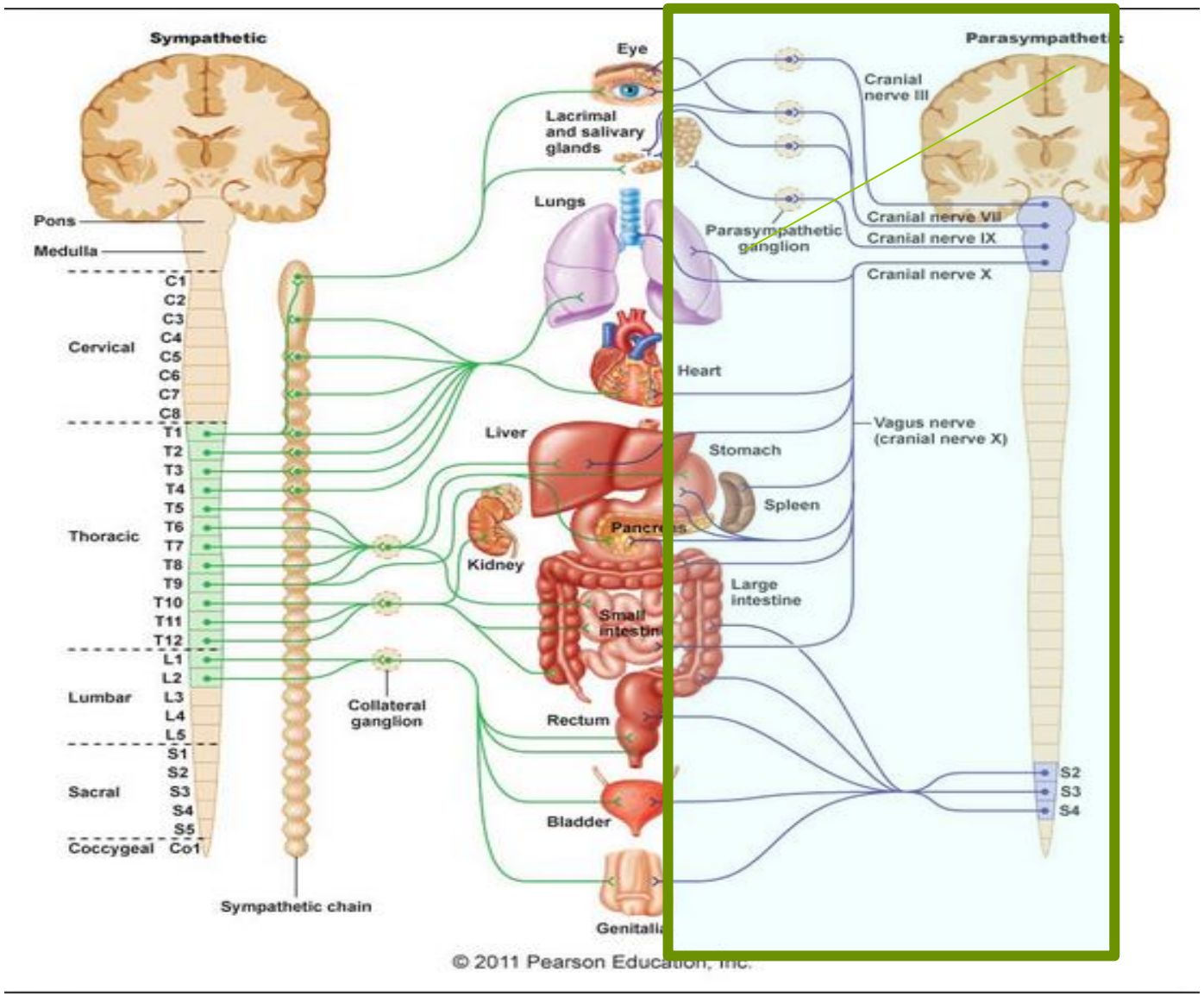


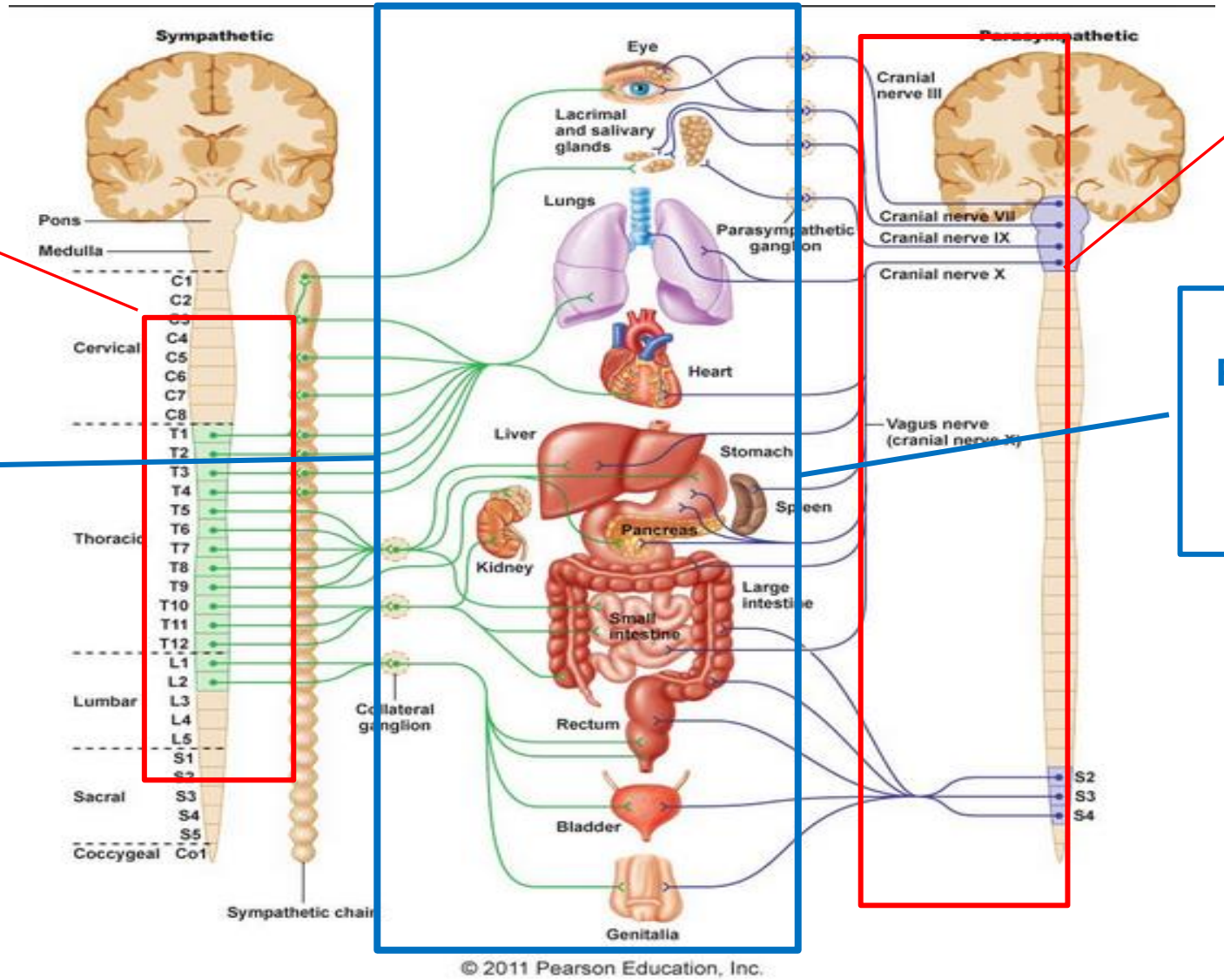
AUTONOMIC NERVOUS SYSTEM (ANS)

Preganglionic
SNS
ACh

Post ganglionic
SNS
NE

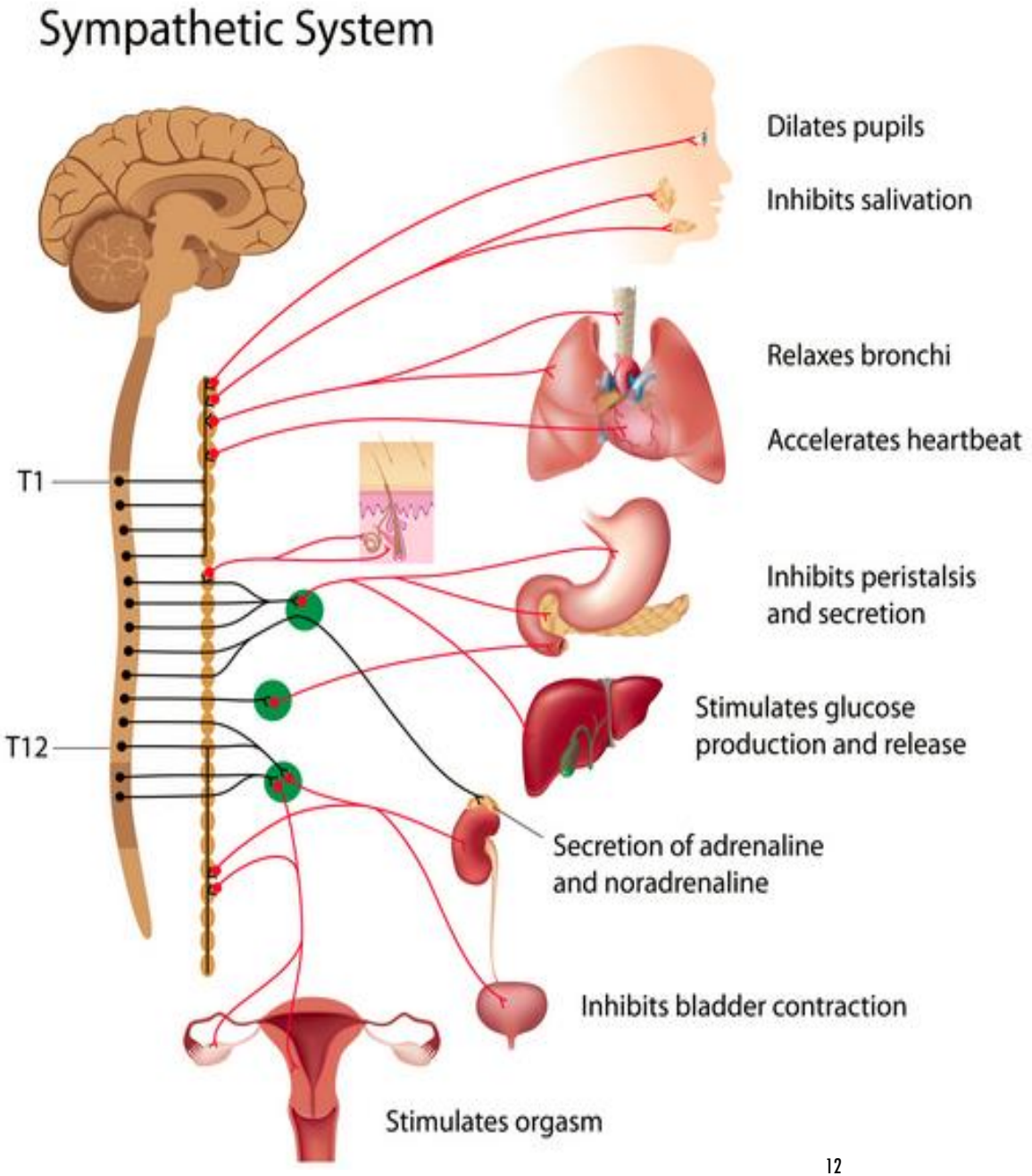
Preganglionic
PNS
ACh

Post ganglionic
PNS
ACh



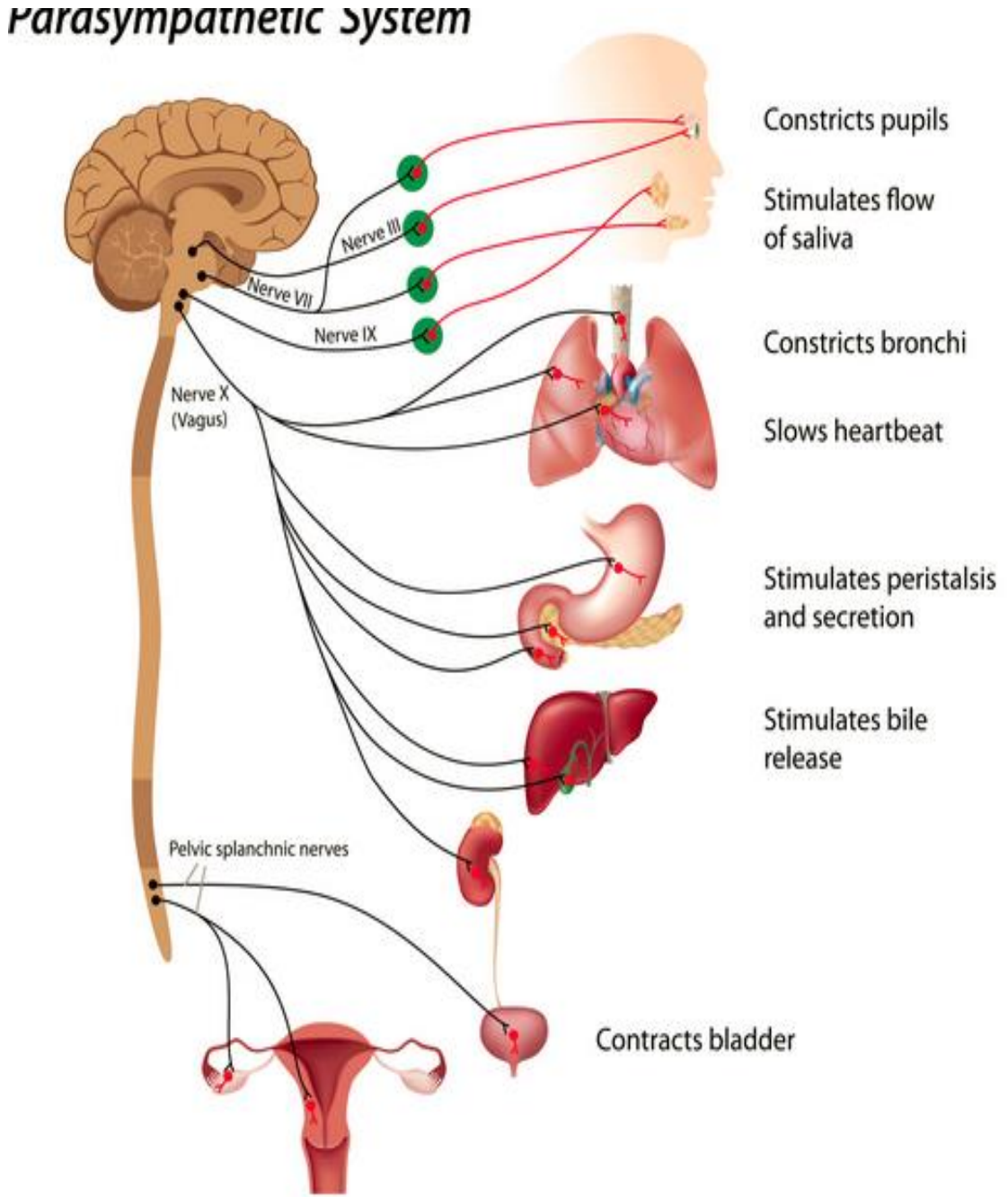
ACTIONS OF THE ANS - SNS

- Think fight or flight
  - Dilate pupils
    - Let in more light to see the bear
  - Inhibit salivation
    - This is no time to be hungry
  - Relax airways
    - Increase O2 intake
  - Increase heart rate
  - …..



ACTIONS OF THE ANS - PNS

- Think rest and digest
  - Constrict pupils
    - Lessened sense of awareness
  - Stimulate saliva
    - Let's eat
  - Constrict bronchi
    - Don't need extra oxygen
  - Decrease heart beat
    - Rest easy

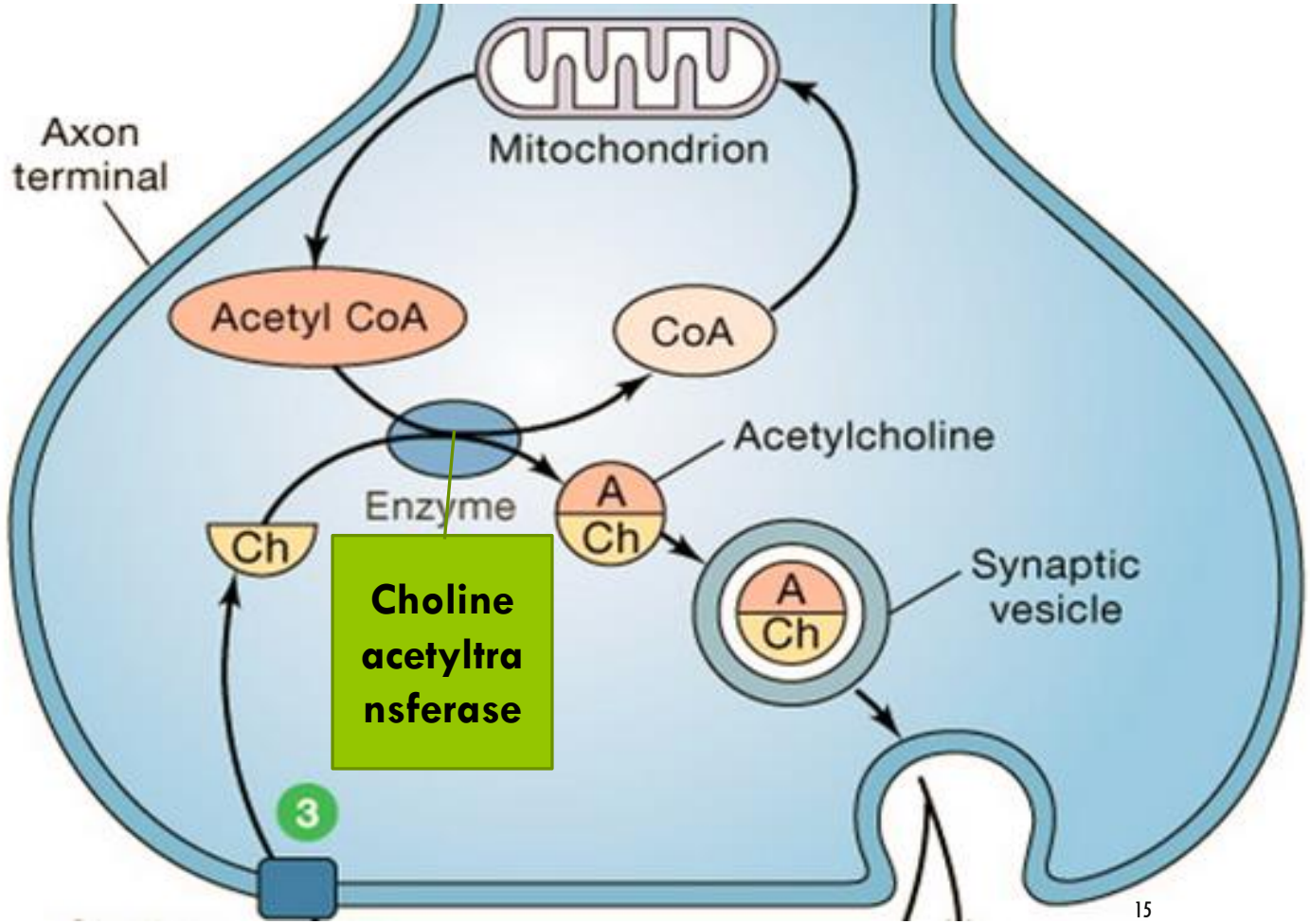


ANS – NEUROTRANSMITTER TRANSMISSION

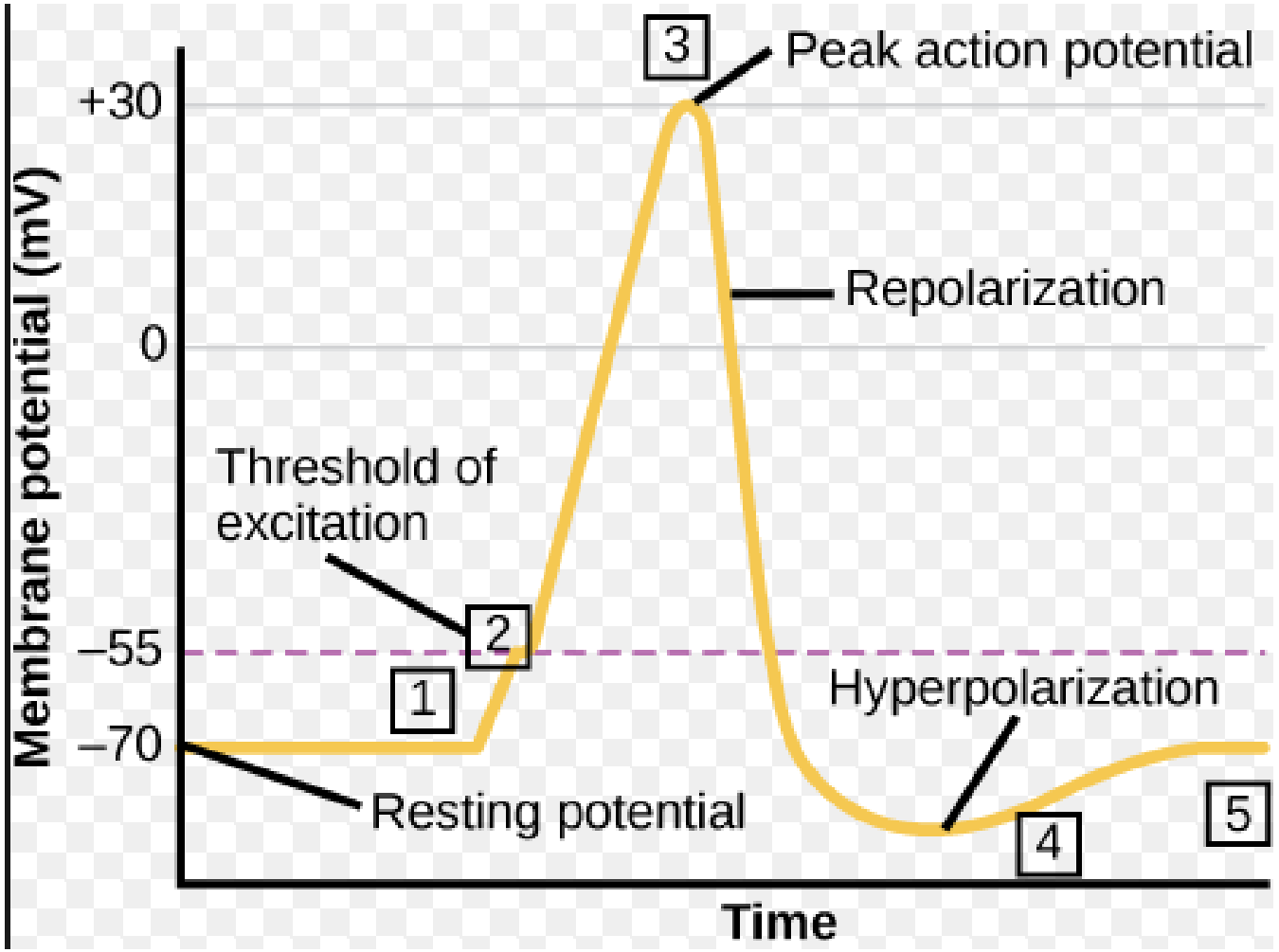
- Cholinergic and adrenergic transmission – from start to finish
  - Synthesis
  - Storage
  - Release
  - Action
  - Inactivation

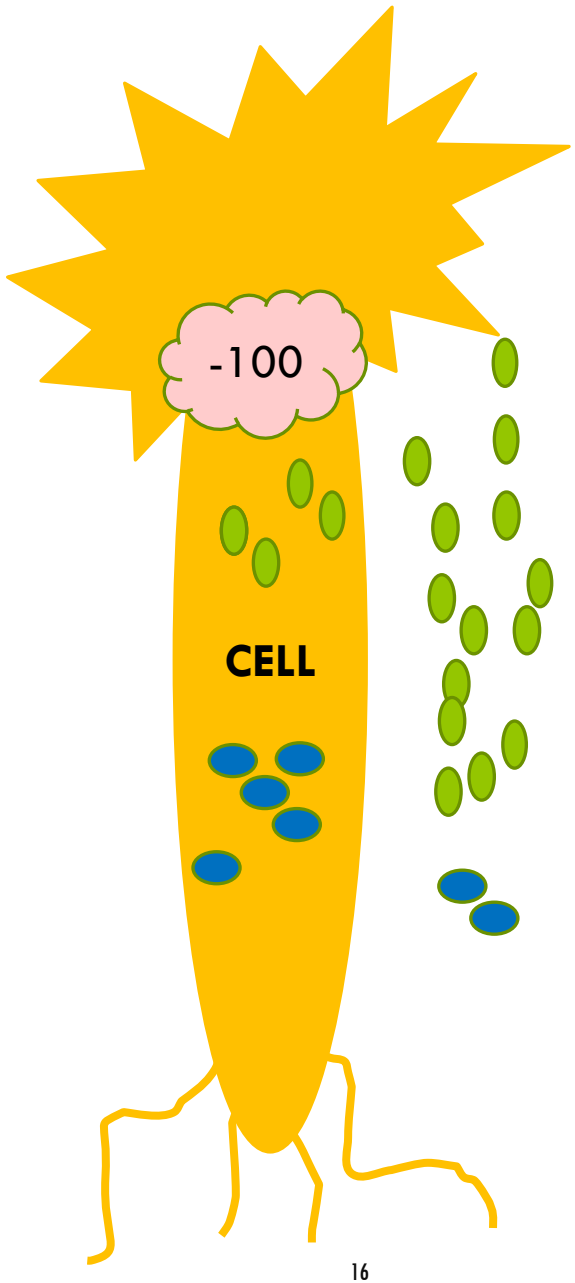
ANS – CHOLINERGIC TRANSMISSION

- Synthesis & Storage



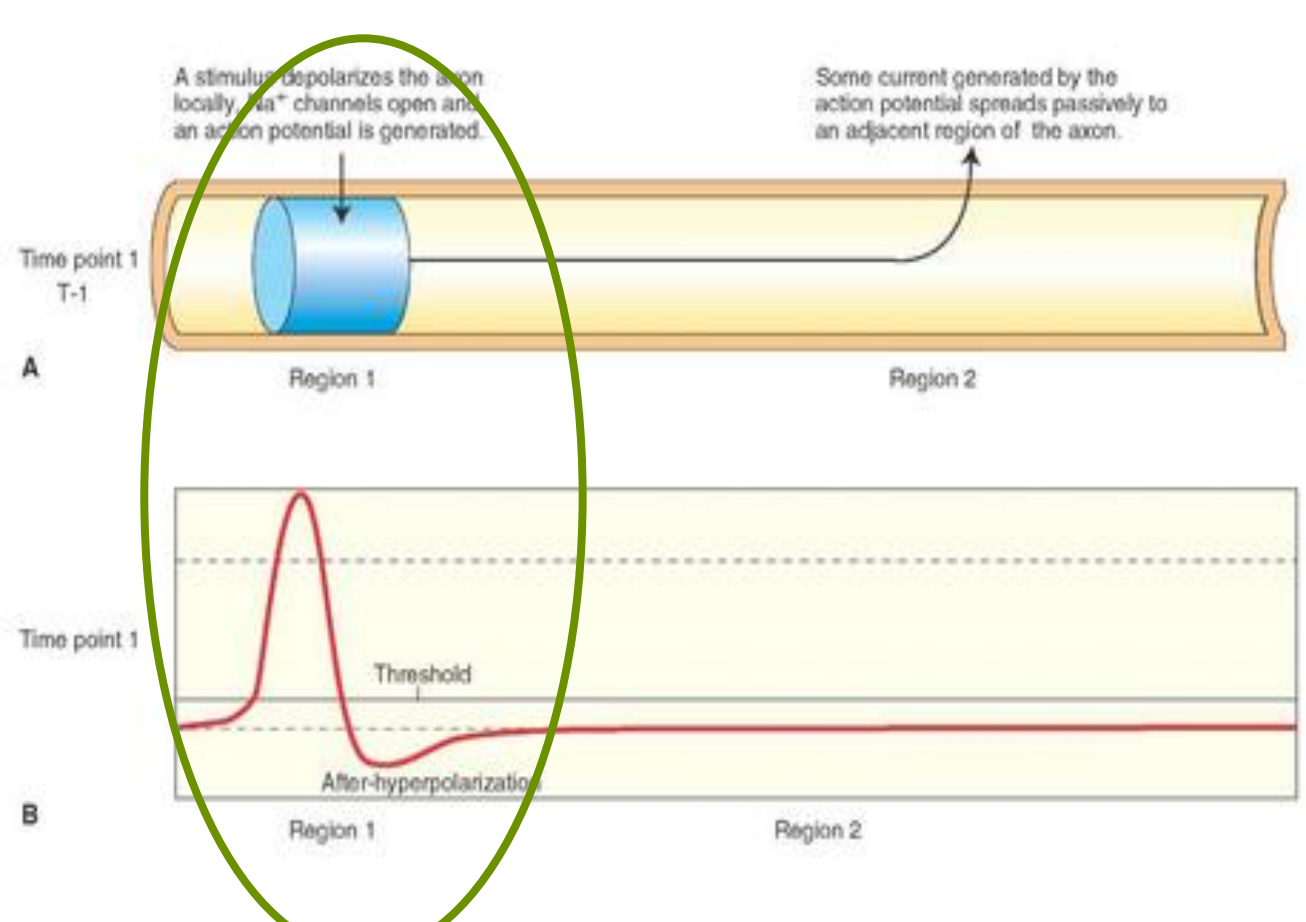
ANS – CHOLINERGIC TRANSMISSION

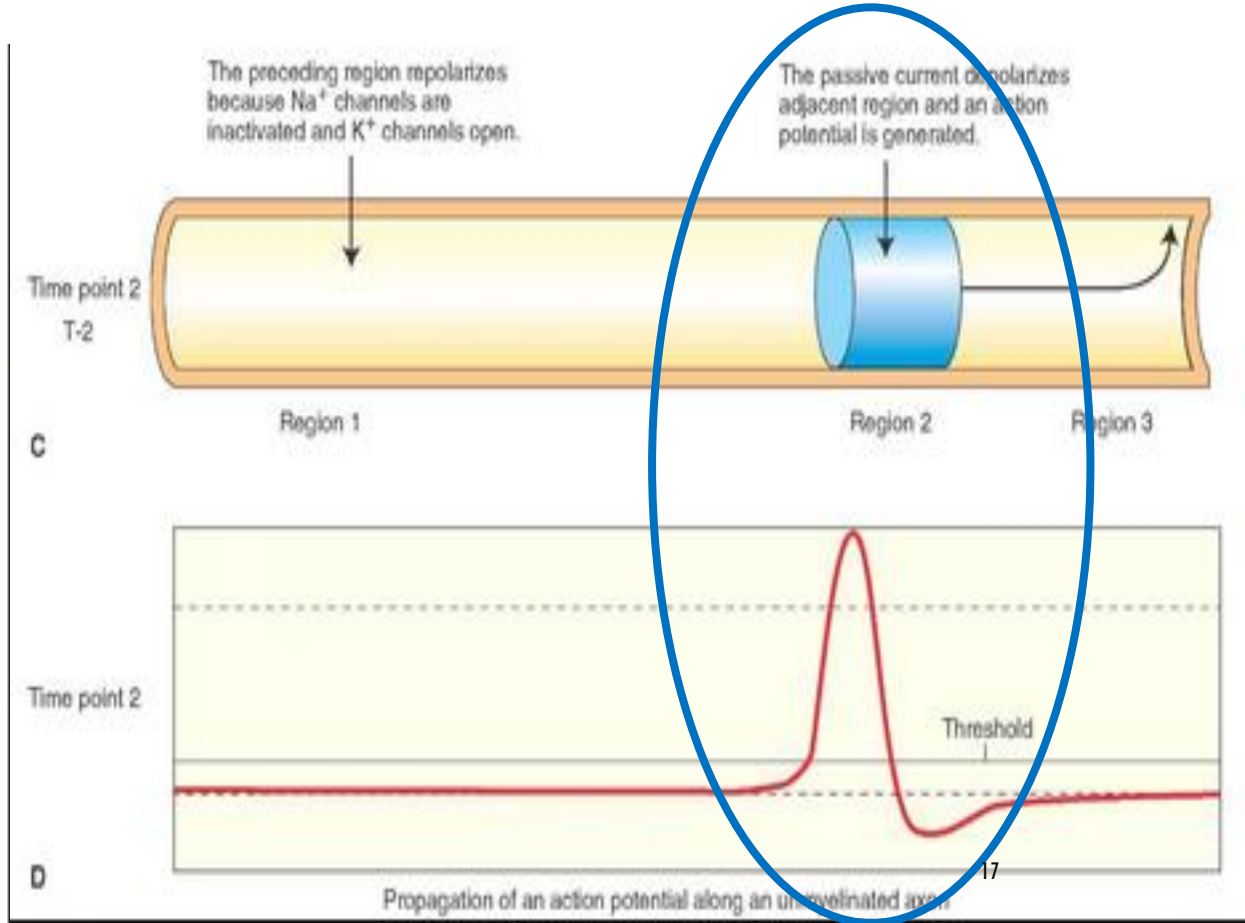




ANS – CHOLINERGIC TRANSMISSION

Propagation





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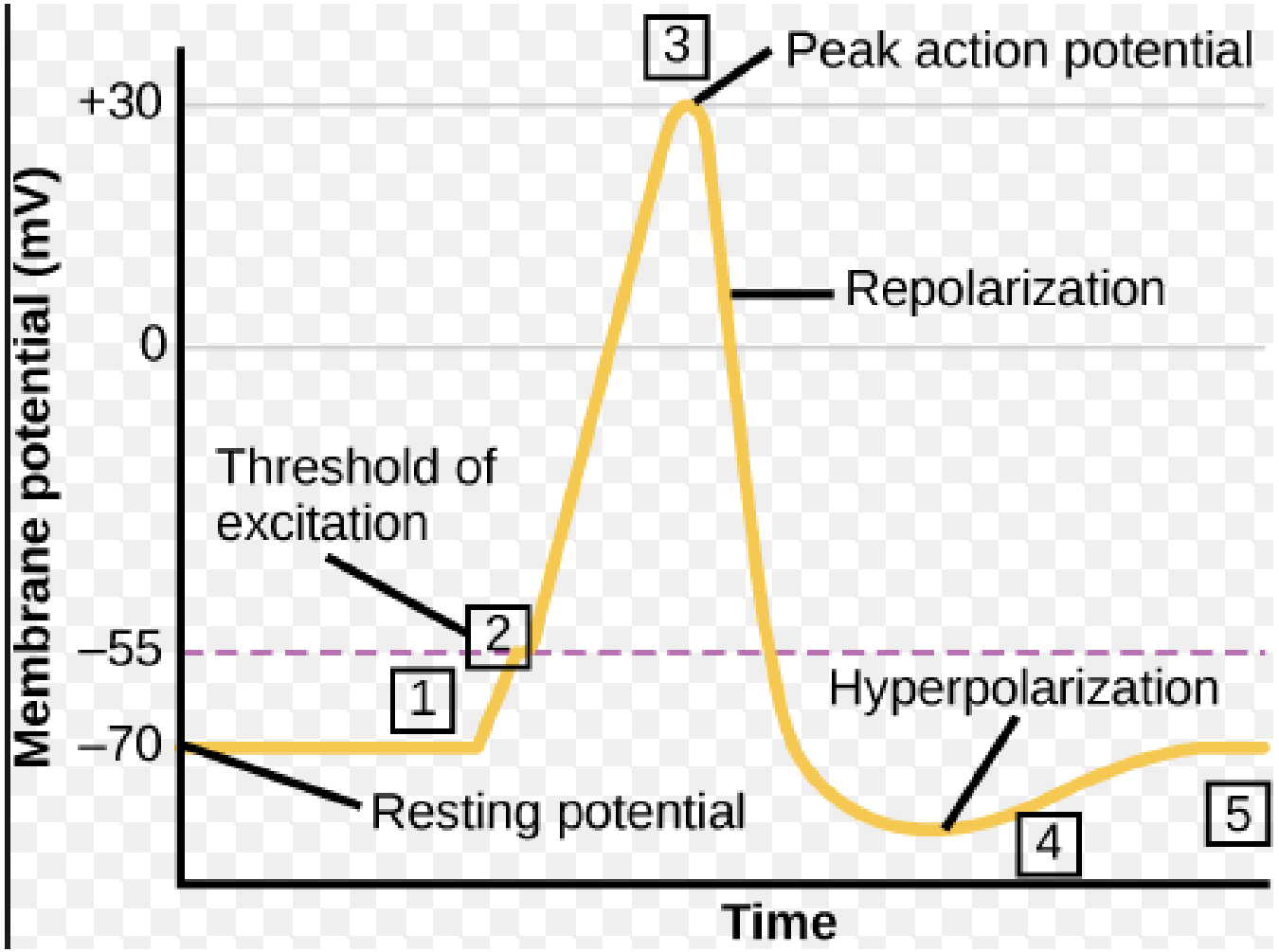

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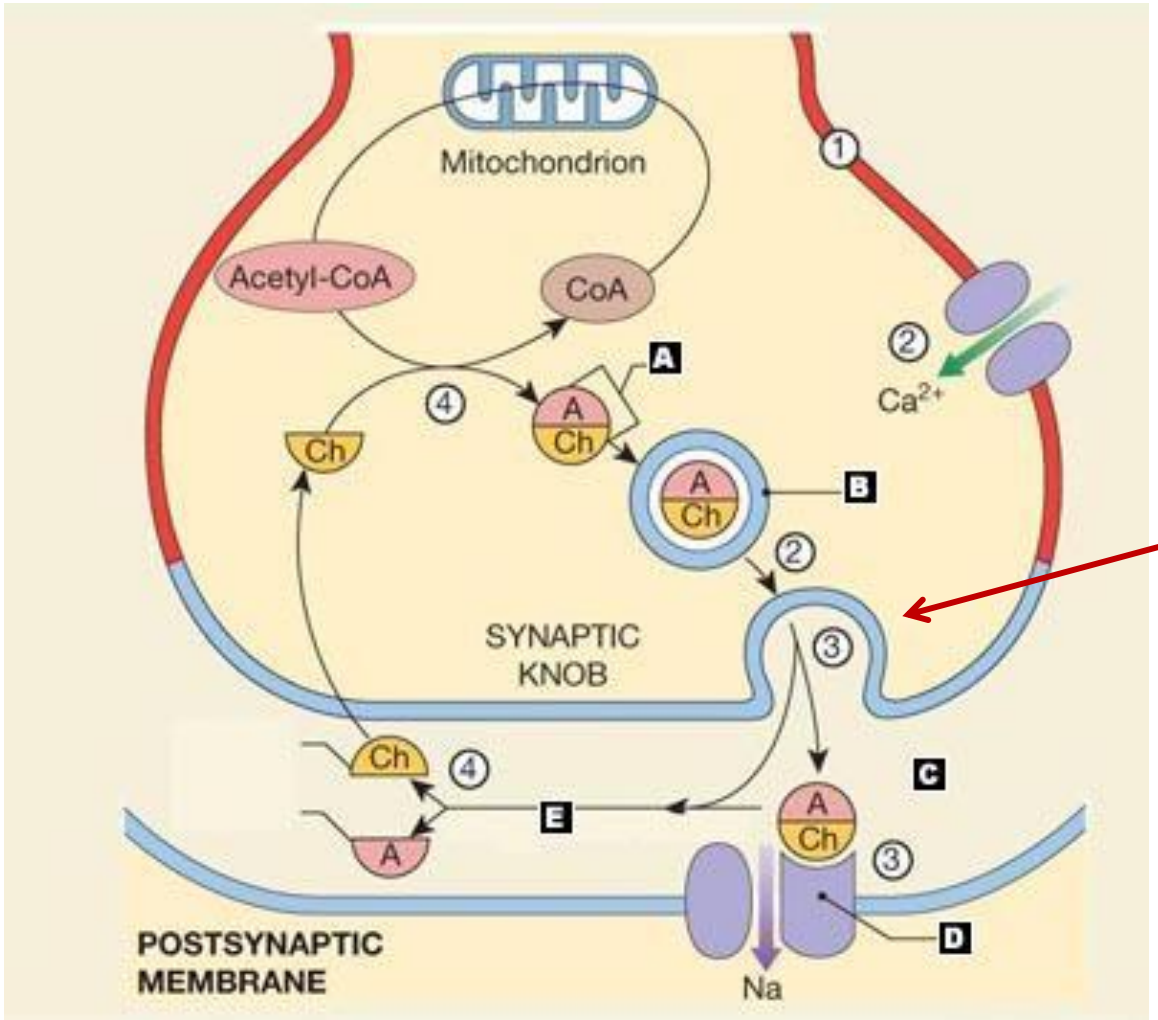
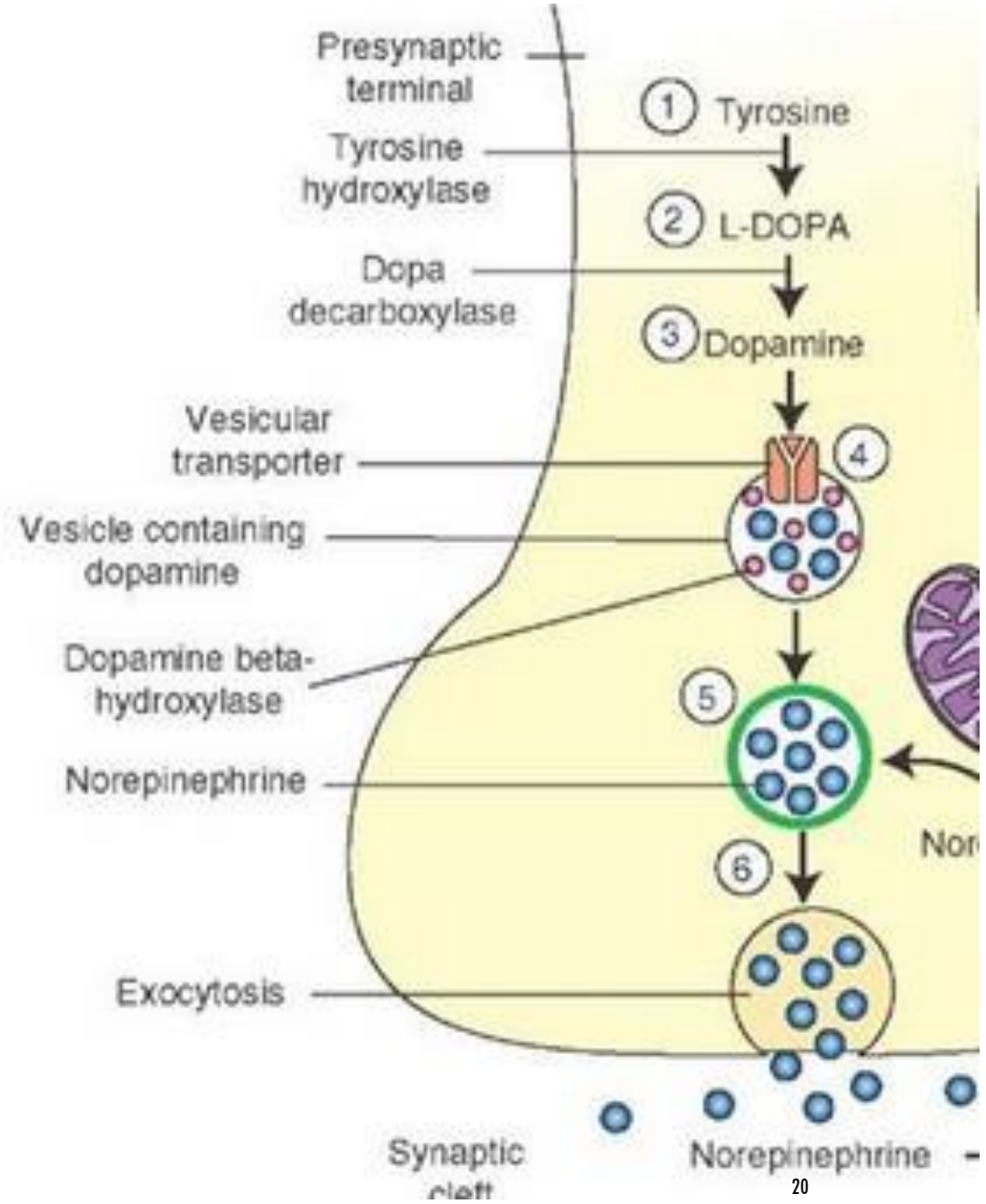


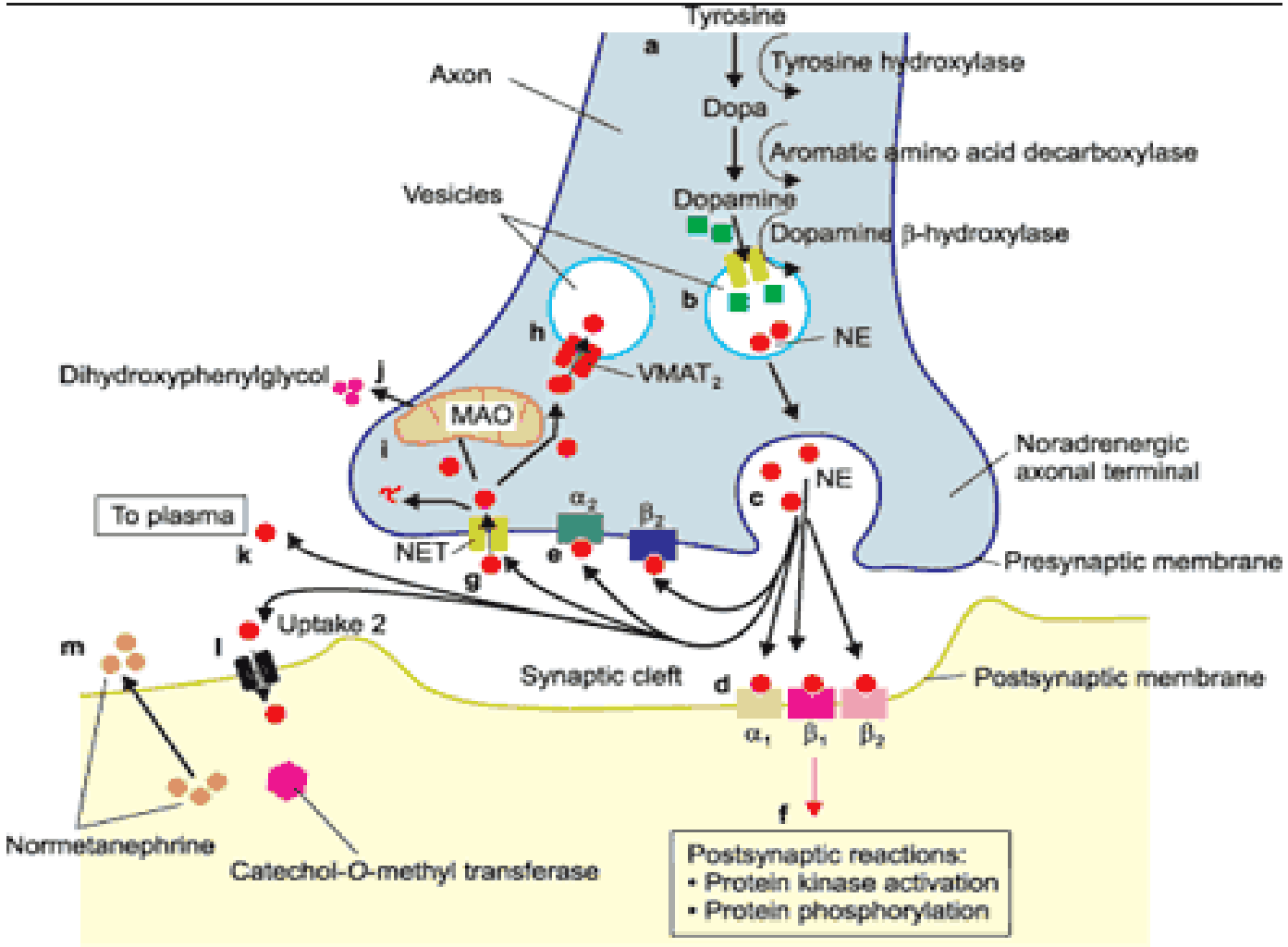
Hey look, exocytosis!

ANS – ADRENERGIC TRANSMISSION

- Synthesis
  - Nerve terminal
    - Neurotransmitter
  - Adrenal medulla
    - Hormone
    - Epi and NE

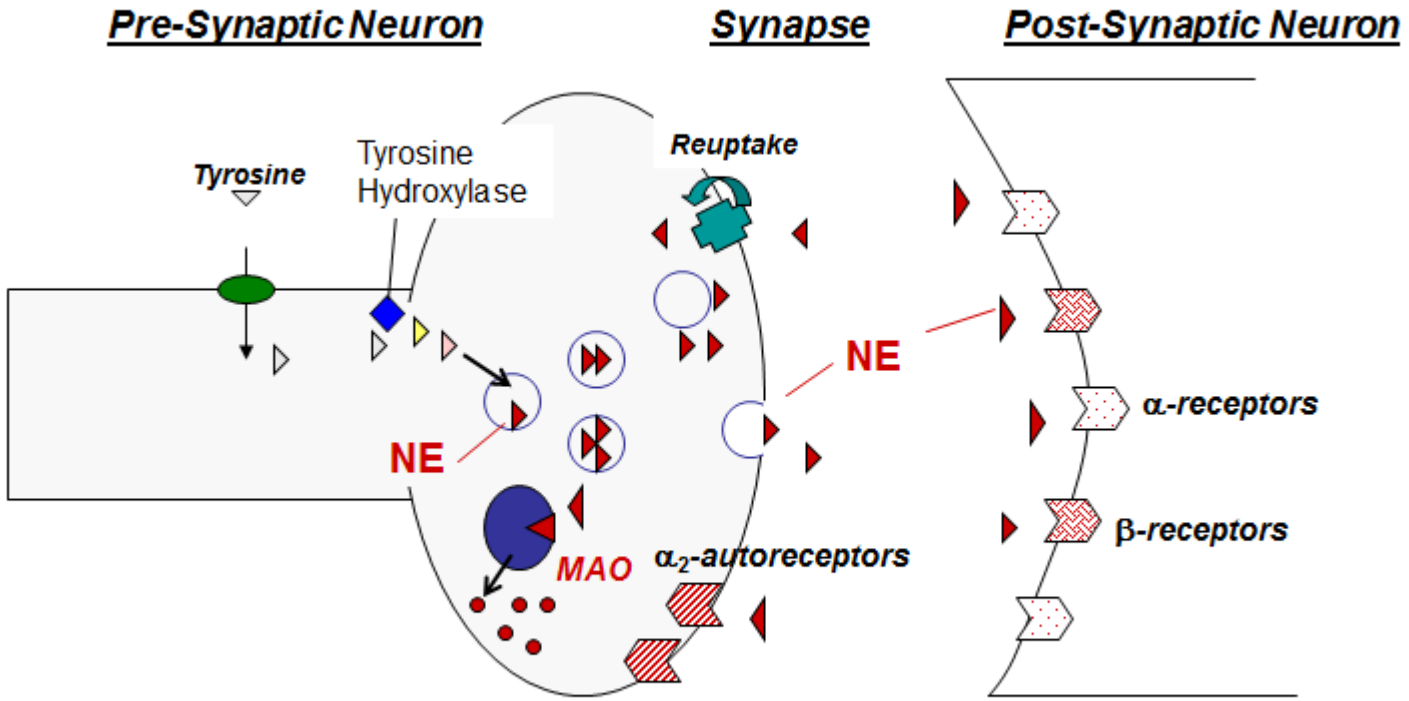


ANS – ADRENERGIC TRANSMISSION



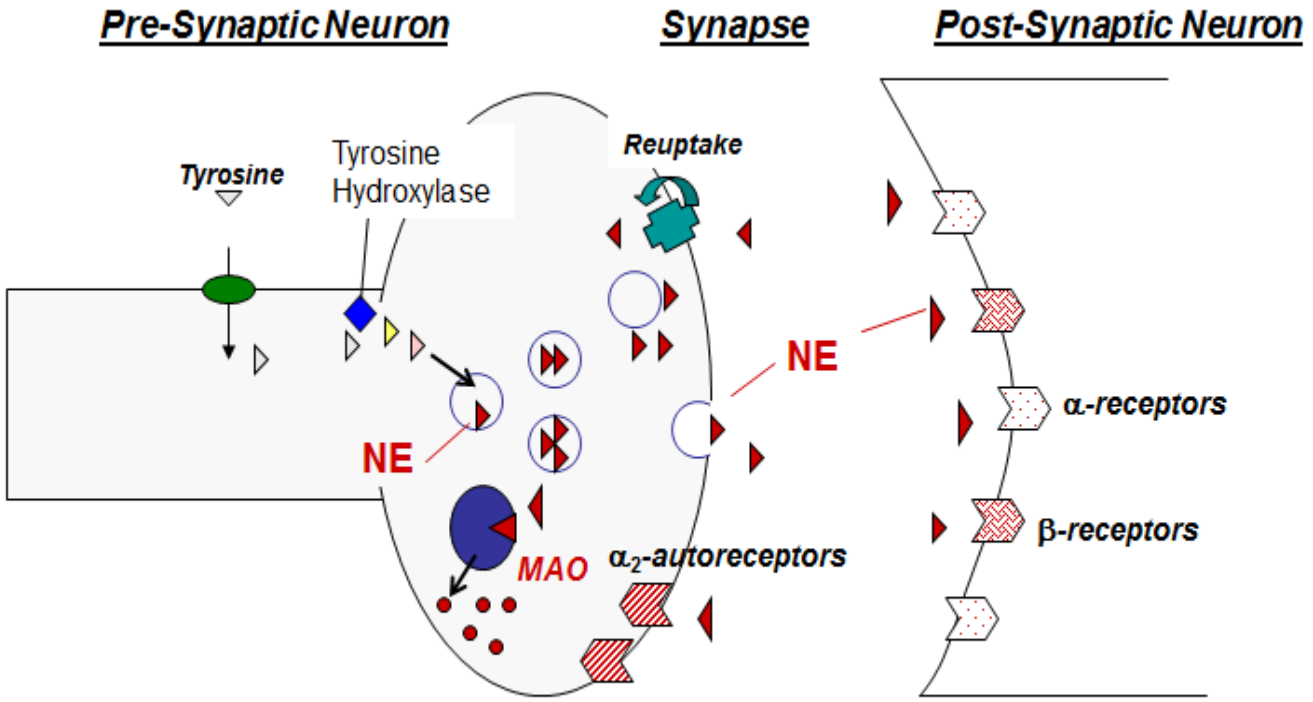
ANS – ADRENERGIC TRANSMISSION

- Alpha receptors - excitatory
  - Alpha 1
    - Postsynaptic nerve
    - Constrict
    - Vascular smooth muscle, prostate, pupillary dilator muscle
  - Alpha 2
    - Presynaptic nerve
    - Inhibit SNS outflow
    - Platelets, adrenergic and cholinergic nerve terminals, some vascular smooth muscle, and fat cells



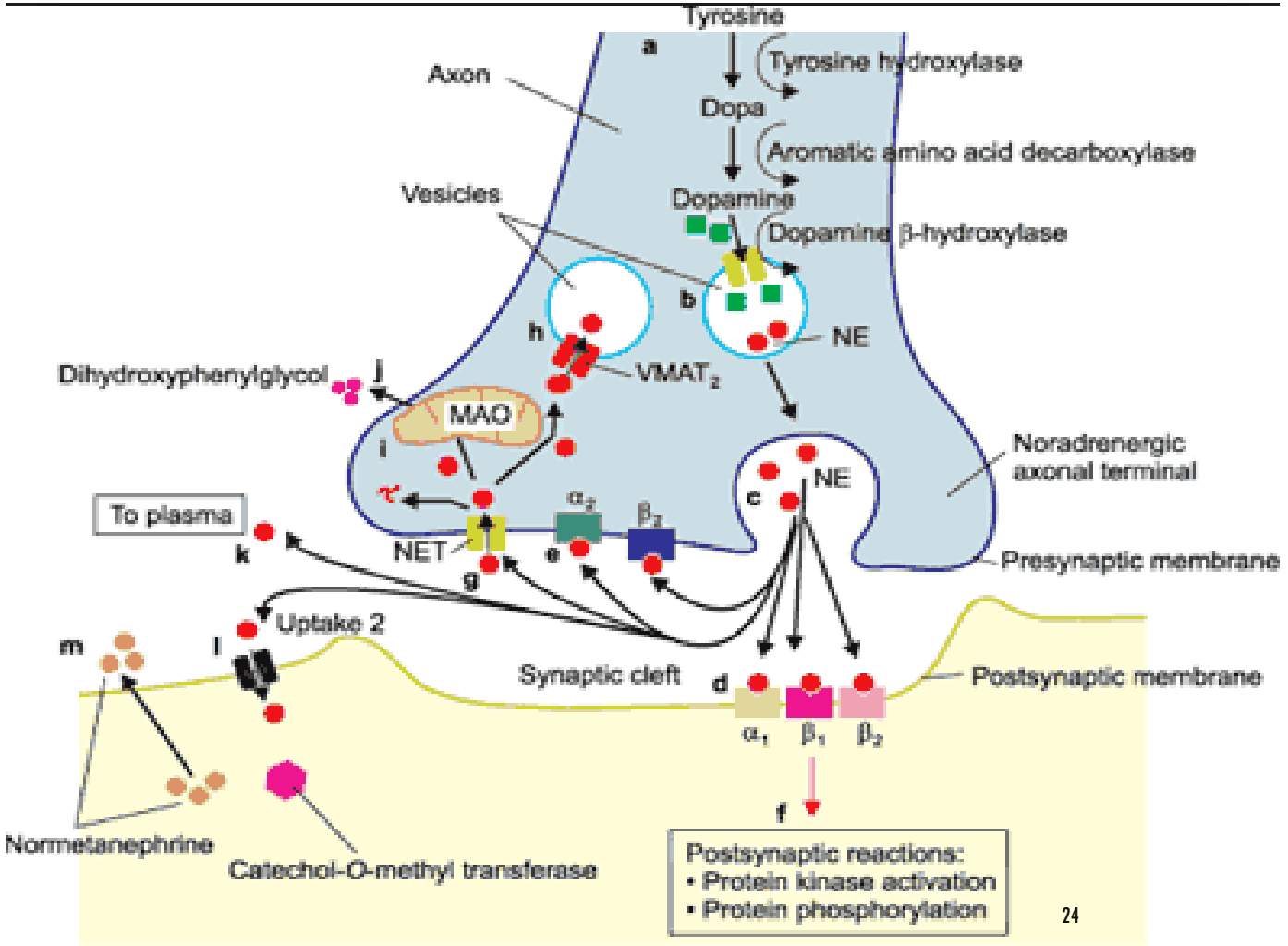
ANS – ADRENERGIC TRANSMISSION

- Beta receptors – inhibitory
  - Beta 1 – heart
  - Postsynaptic
  - Increase rate & increase force of contraction
- Beta 2 – lungs
  - Postsynaptic
  - Relax & increase glucose
  - Lungs, liver, & vascular smooth muscle



ANS – ADRENERGIC TRANSMISSION

- Turning off the SNS
  - Reuptake
  - Monoamine oxidase (MOA)
  - Catechol-o-methyltransferase (COMT)



AUTONOMIC NERVOUS SYSTEM - SUMMARY

- The 2 branches of the ANS are the SNS and PNS
- The PNS and SNS balance each other out in terms of daily activities
- Each of these systems has its own set of NTs and receptors with actions that promote its cause and attenuate the cause of its brother system

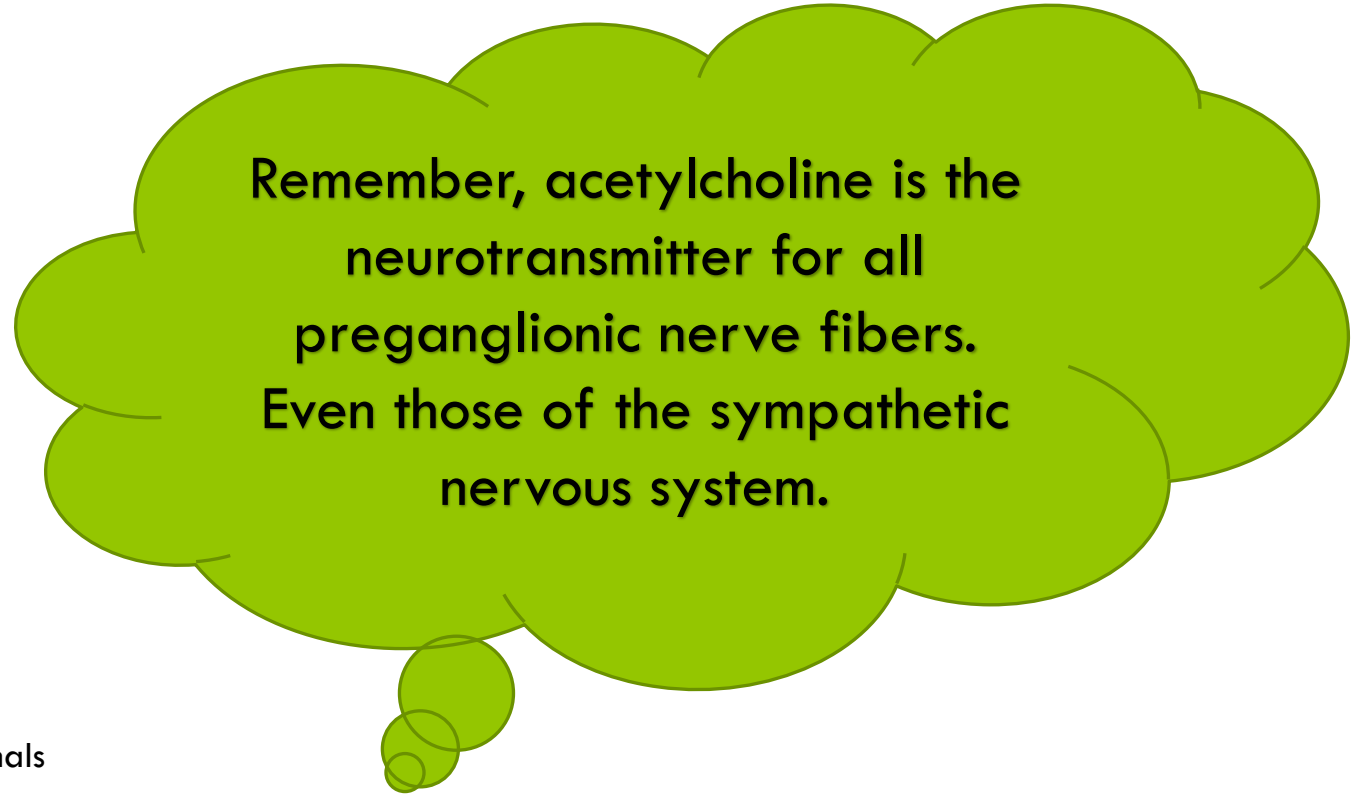
QUESTIONS

LEARNING OBJECTIVES – CHOLINERGIC AGONISTS

- Know the receptor location and neurotransmitter involved in direct acting and indirect acting drugs of the cholinergic agonist class
- Know the physiologic results of the activation or inhibition of those receptors
- Know the dosage forms involved in nicotine replacement therapy (NRT)
- Know the toxic effects of cholinergic agonists & acetylcholinesterase inhibitors

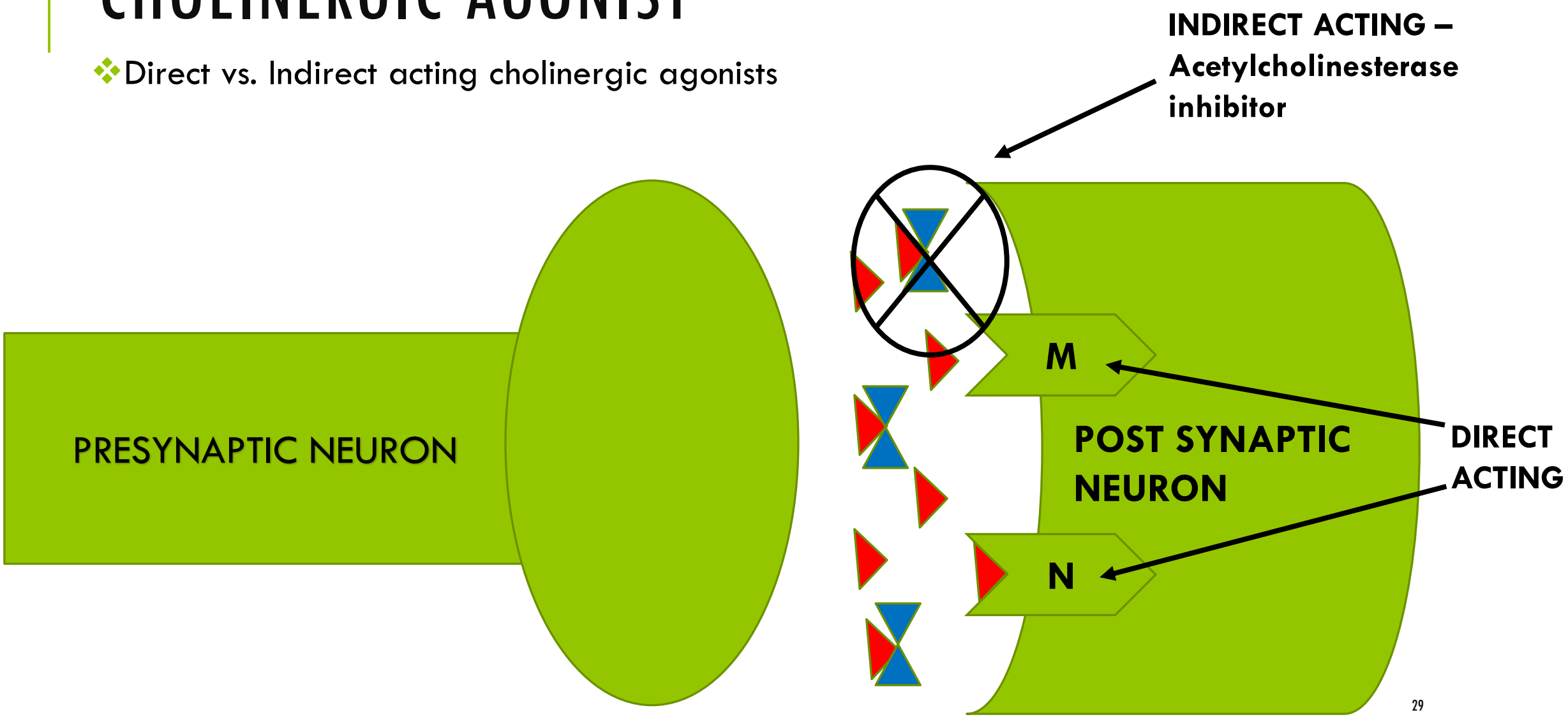
CHOLINERGIC AGONIST

- Parasympathomimetic
- Receptors
  - Nicotinic
    - Ganglia, adrenal medulla, skeletal muscle, brain
  - Muscarinic
    - Cardiac and smooth muscle, gland cells, and nerve terminals



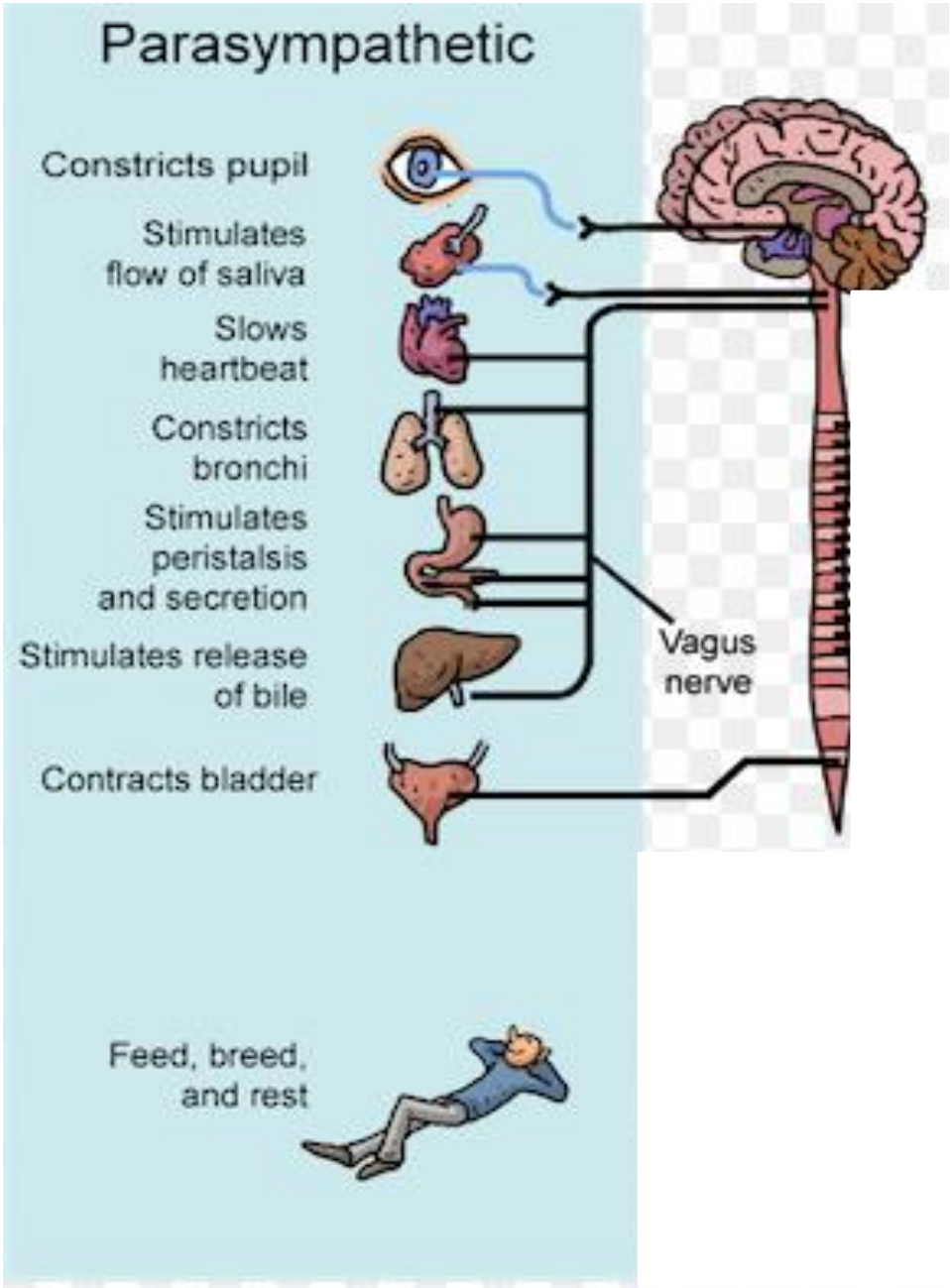
CHOLINERGIC AGONIST

- Direct vs. Indirect acting cholinergic agonists



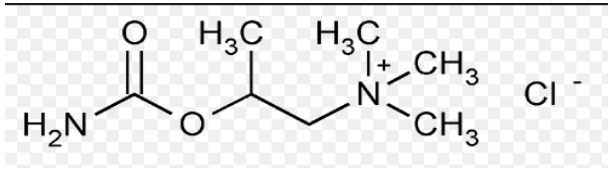
MUSCARINIC RECEPTORS

- Muscarinic receptors
  - Eye (lacrimal gland), saliva gland, heart, lungs, GI tract, gallbladder, bladder, AND sweat glands (sympathetic effect) AND vascular smooth muscle (no PNS innervation)



MUSCARINIC AGONISTS – DIRECT ACTING

- **Bethanechol**



- Brand name: Urecholine
- Use: Ease urinary retention in the neurogenic bladder
- Dosage form: Oral tablet
- Distribution: Poorly absorbed and poorly distributed to CNS, concentrates in GI tract and bladder
- MOA: Increase bladder muscle tone, stimulated gastric motility
- Onset/Duration: 30-90 min/~1 hr (up to 6 hrs)
- ADRs:
  - Cardiovascular
    - Hypotension, flushing, tachycardia
  - CNS
    - Headache, malaise, seizure
  - Dermatology
    - Sweating
  - GI
    - Abd. cramps, diarrhea, burping, rumbly tummy, nausea, salivation, vomiting
  - GU:
    - Urinary urgency
  - Ophthalmic
    - Miosis & lacrimation
  - Respiratory
    - Bronchoconstriction/asthma
- Overdose: Treat with atropine

MUSCARINIC AGONIST– DIRECT ACTING

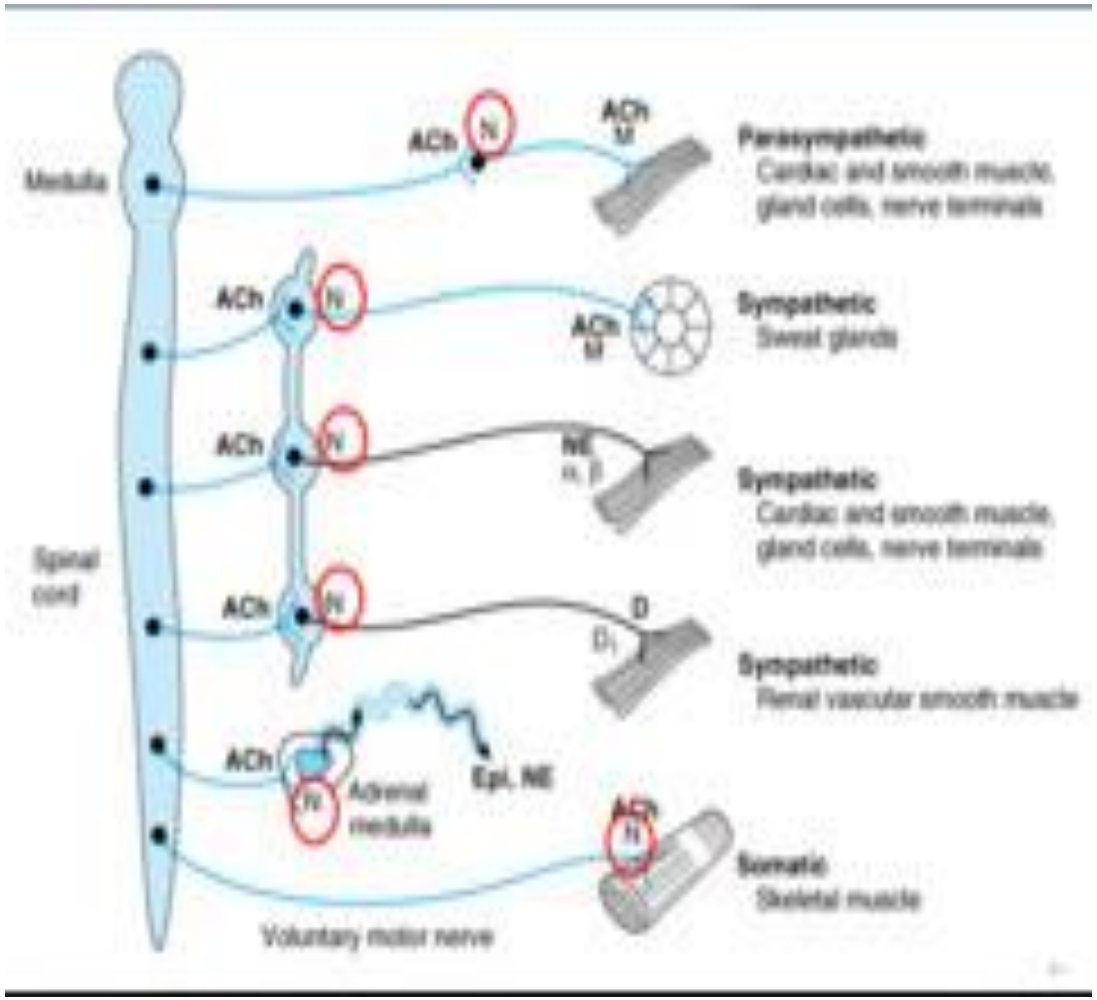
- **Pilocarpine**

- Brand name: Salagen (oral)/Isopto Carpine (ophthalmic)
- Use: Xerostomia (cancer tx/sjogrens), glaucoma
- Dosage form: Tablet/solution & gel
- Distribution: Well absorbed and distributes into the CNS
- MOA: Increased salivation/miosis, decreased intraocular pressure
- Onset/Duration: 10-60 min/ 4-8 hrs (up to 12 hrs)
- Excretion: Kidney

- ADRs:
  - Cardiovascular
    - flushing
  - CNS
    - Headache
  - Dermatology
    - Rash, itching
  - GI
    - Nausea
  - GU:
    - Urinary frequency
  - Ophthalmic
    - Double vision & lacrimation
  - Respiratory
    - Rhinitis

NICOTINIC RECEPTORS

- Nicotinic receptors
  - Ganglia, adrenal medulla, skeletal muscle, and neuronal cells in the CNS
- CNS effects
  - At therapeutic doses – mild alerting effect
  - At increased to toxic doses – tremor, stimulation of respiratory center, convulsions, & coma
- Neuromuscular junction
  - At therapeutic doses – contraction of muscle
  - At increased to toxic doses – disorganized twitching, contraction of entire muscle, & paralysis
- Peripheral nervous system
  - Activation of the SNS and PNS at the same time
    - Cardiovascular effects – mostly SNS effects
    - GI tract – mostly PNS effects



NICOTINIC AGONISTS – DIRECT ACTING

Nicotine (NRT)

- Use: Smoking cessation
- Dosage forms: Next slide
- Distribution: Lipophilic, distributes well to tissues
- Onset/duration: Fast/24 hour – depends of dosage form
- Metabolism: Liver
- Excreted: Kidney
- ADRs: Depends on dosage form – headache, nausea, throat irritation, cough, dyspepsia
- Toxicity: Very toxic. Lethal doses seen at 30-60 mg (5 cigarettes)

Varenicline (Chantix)

- Use: Smoking cessation
- Dosage forms: Tablets – Can be dispensed in monthly packs
- Distribution: Well absorbed, not affected by food, 90% bioavailability
- Onset: Peak 3-4 hours
- Half-life: 24 hours
- Excretion: Urine 92% unchanged drug
- ADR's:
  - CNS – HA, insomnia, abnormal dreams, suicide ideation, depression (can lead to d/c)
  - GI: Nausea and vomiting

NRT – DOSAGE FORMS

Product	Nicotine Dosage	Adverse Effects	Usage
Patch	7, 14, or 21 mg/d	Skin reactions, vivid dreams, insomnia	Patch is placed on skin; user reduces dosage over time
Gum	2 mg or 4 mg every 1-2 h	Hiccups, nausea, jaw pain	User chews gum until it produces a tingling feeling, then parks gum between cheek and gum and chews with cravings
Lozenges	2- or 4-mg lozenge as needed with cravings	Hiccups, nausea, heartburn	User places lozenge in mouth where it dissolves slowly
Inhaler	4 mg/cartridge, 6-16 cartridges/d	Throat irritation, mouth irritation, nasal congestion, cough	Inhalation through mouthpiece delivers nicotine
Nasal spray	1 spray (0.5 mg) per nostril per hour as needed with cravings	Nasal irritation, nasal congestion, changes in taste and smell	Inserted and sprayed into each nostril; used to control cravings fast for heavy smokers

CHOLINERGIC AGONIST – INDIRECT ACTING

Neostigmine

Pyridostigmine

Ambenonium

Physostigmine

Tacrine

Donepezil

Rivastigmine

Galantamine

Myasthenia gravis: Autoimmune disease that degrades nicotinic receptors from autoantibodies causing severe muscle weakness.

GI & GU disorders: Post operative ileus, congenital megacolon, urinary retention, reflux esophagitis

Antimuscarinic overdose: Plants, atropine, 1st generation antihistamines, & tricyclic antidepressants. Physostigmine completes with the antimuscarinic agent. Only used with high fever or supraventricular tachycardia

Alzheimer's disease: Degradation of cholinergic nerves in CNS causing memory loss and cognitive function decline Causes not known: Efficacy of these drugs is modest and doses and use are limited by adverse effects.

ACETYLCHOLINESTERASE INHIBITOR EFFECTS

Type of effects	Lower doses	Higher doses

Autonomic effects	• Nicotinic receptor activation
	  ○ SNS & PNS effects
	  ○ Decreased HR and BP
	• Muscarinic receptor activation
	  ○ Miosis/impaired vision
	  ○ Bronchospasm/increased secretions
	  ○ Sweating/salivation
	  ○ Nausea/vomiting
	  ○ Diarrhea/abd cramps
	  ○ Urination
		*Both SNS and PNS are activated but the effects of the PNS prevail. Patient will present with bradycardia, reduced cardiac output, variable blood pressure, severe bronchospasm, reduced respiratory function.
		• SLUDGE
		  ○ Salivation, lacrimation, urination, diarrhea, GI upset, emesis
		• DUMBELS
		  ○ Diaphoresis & diarrhea, urination, miosis, bradycardia/bronchospasm/bronchorrhea, emesis, lacrimation, salivation

Central NS effects	• Nicotinic & muscarinic receptor activation
	  ○ Anxiety/confusion
	  ○ Tremors
		• Nicotinic & muscarinic receptor activation
		  ○ Tremors/seizures
		  ○ Coma
		  ○ Depression of respiratory center

Motor effects	• Nicotinic receptor activation on skeletal muscle
	  ○ Muscle twitching and weakness
		• Nicotinic receptor activation on skeletal muscle
		  ○ Paralysis
		  ○ Respiratory failure

ACETYLCHOLINESTERASE INHIBITOR OVERDOSE

- Lethal – due to respiratory effects
- Usually due to poisoning, chemical warfare, insecticides (organophosphates)
- Route – skin or lungs.
- First signs – Ocular symptoms followed by respiratory symptoms
- Treatment
  - Ventilation
  - ATROPINE
  - Pralidoxime (reactivated enzymes)

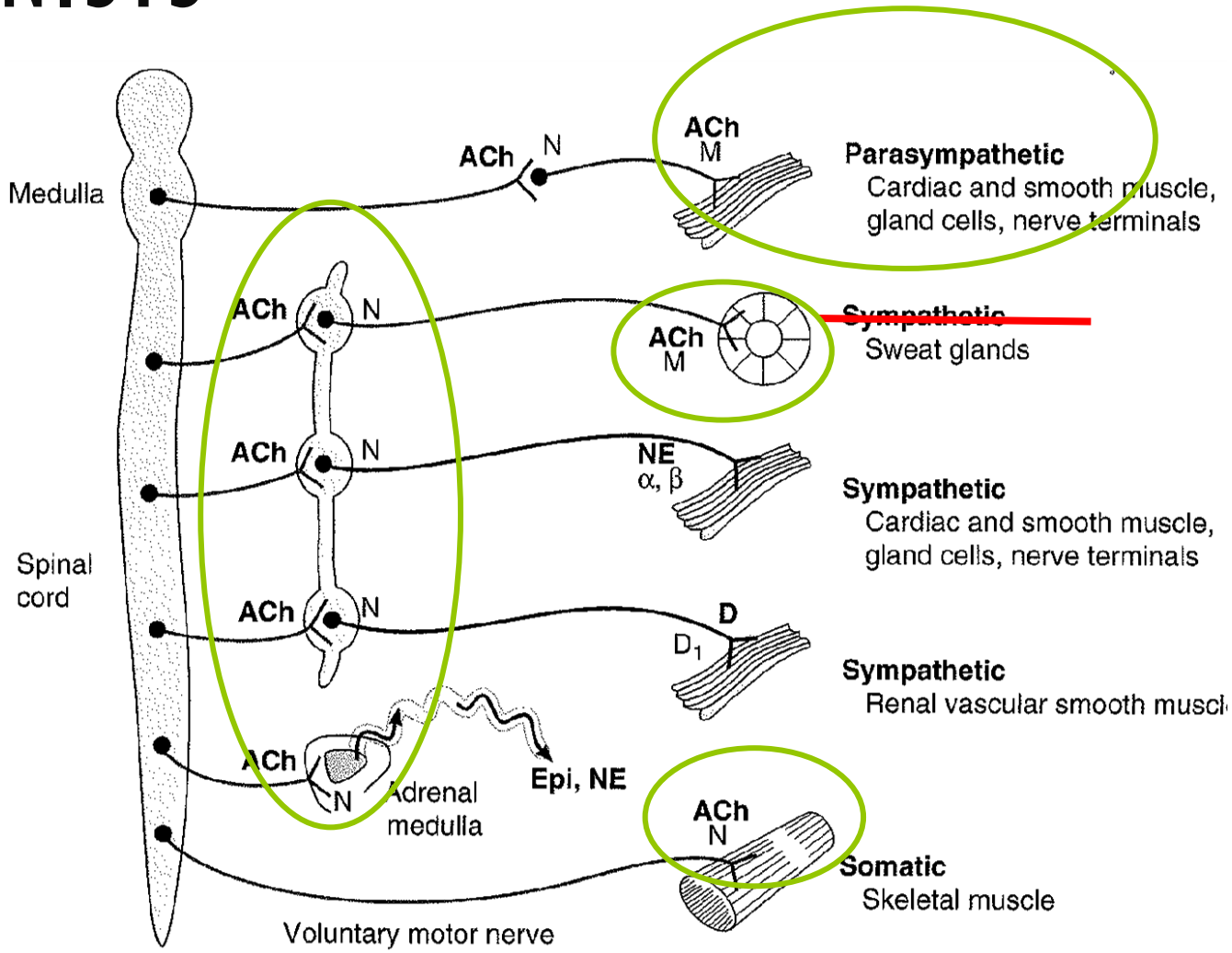
QUESTIONS

LEARNING OBJECTIVES – CHOLINERGIC ANTAGONISTS

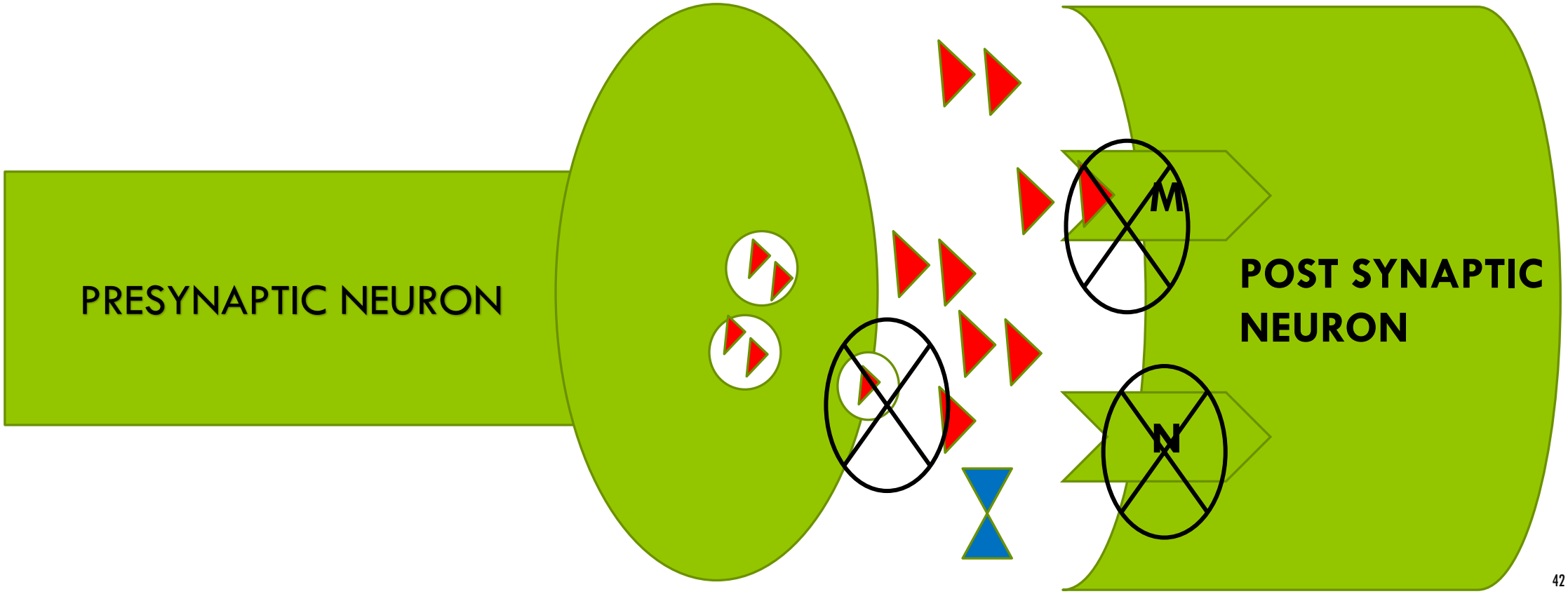
- Know the receptor location and neurotransmitter involved in direct acting and indirect acting drugs of the cholinergic agonist class
- Know the physiologic results of the activation or inhibition of those receptors
- Know the general therapeutic uses for the cholinergic antagonists class of medications
- Know antidotes
- Know the toxicities related to the overuse of cholinergic antagonists

CHOLINERGIC ANTAGONISTS

- Antimuscarinics and Antinicotinics
- Parasympatholytics
- Receptors
  - Muscarinic
    - Cardiac and smooth muscle, gland cells, and nerve terminals
    - Sweat glands – sympathetic
  - Nicotinic
    - Ganglia & skeletal muscle



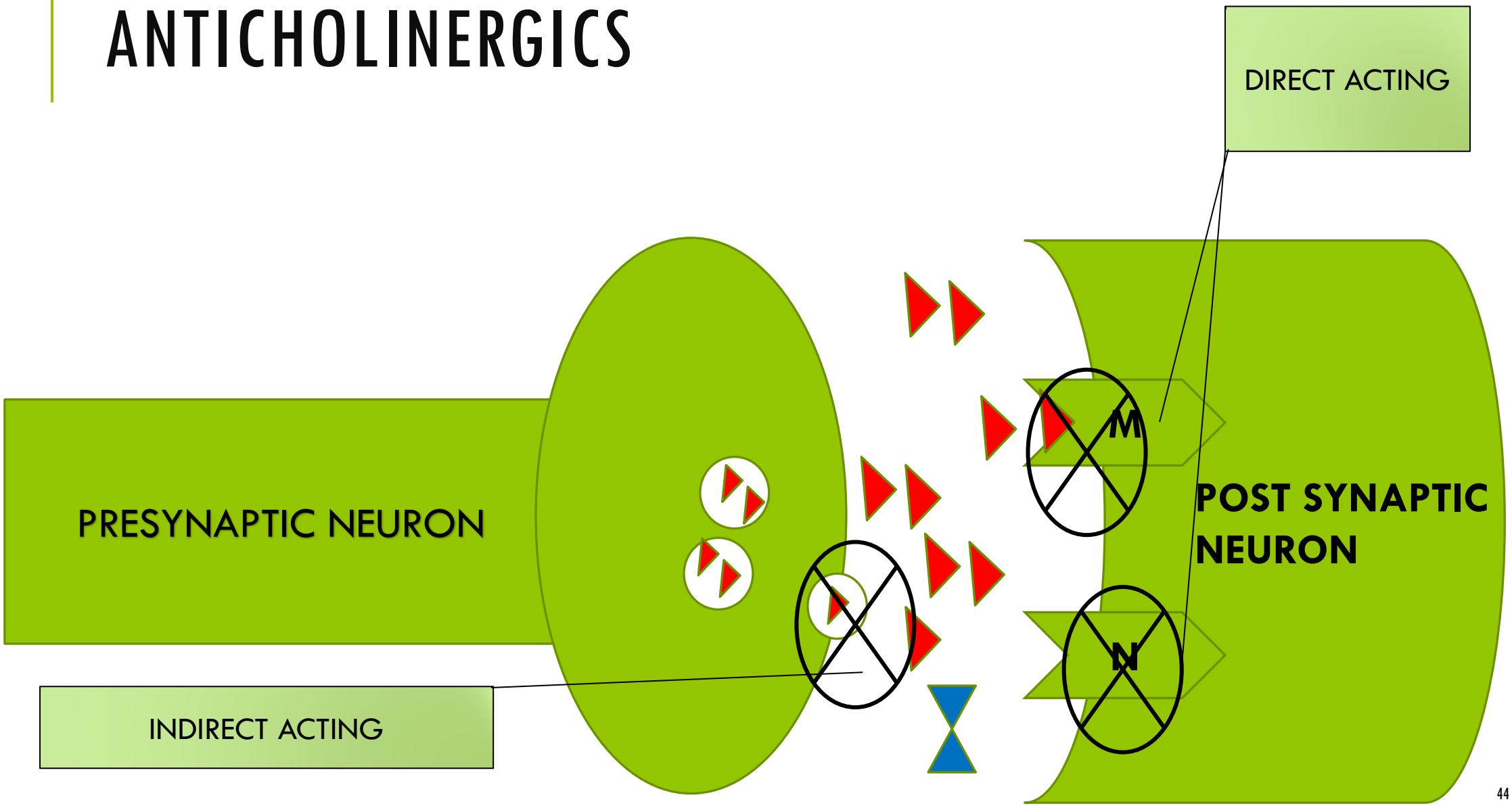
ANTICHOLINERGICS



ANTICHOLINERGICS

Which of those pathways represents a direct acting drug and which represents an indirect acting drug?

ANTICHOLINERGICS

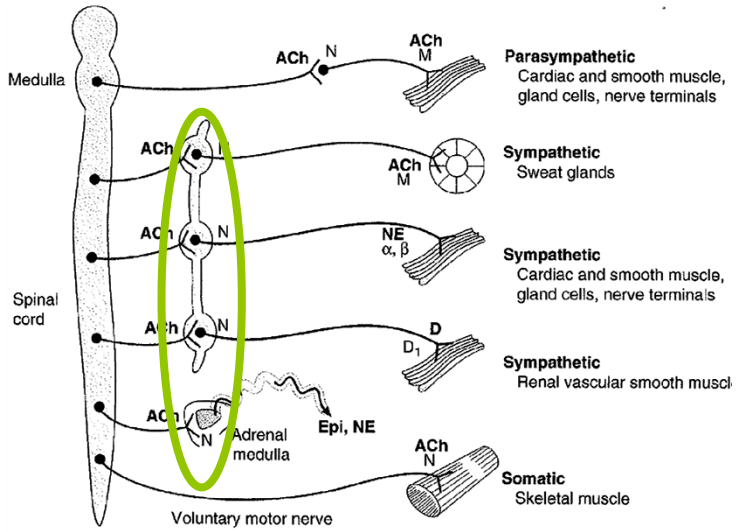


ANTICHOLINERGICS – @ THE GANGLIA & ADRENAL MEDULLA

- Decreased concentrations of epinephrine and norepinephrine & antagonism of acetylcholine

- Parasympathetic
  - Constipation, tachycardia, dry mouth, nausea, vomiting, angina, urinary retention, impotence

- Sympathetic
  - Decreased blood pressure, decreased release of epinephrine and norepinephrine, decreased sweating,

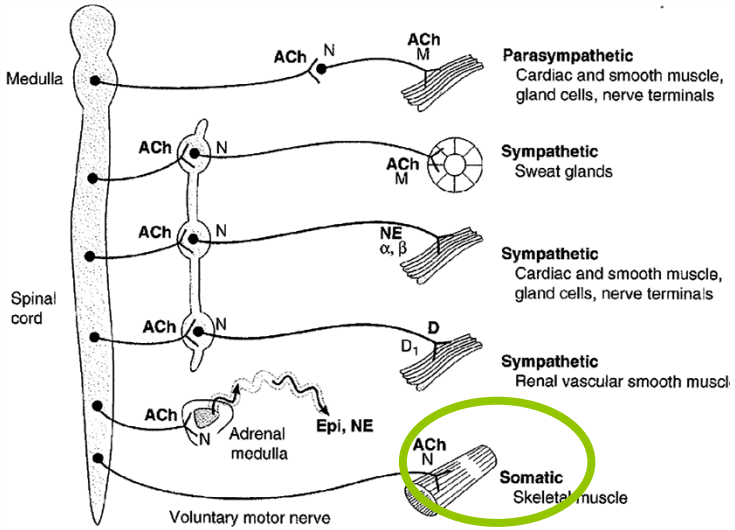


ANTICHOLINERGICS – @ THE GANGLIA & ADRENAL MEDULLA

- When do we use these medications:
  - HYPERTENSIVE EMERGENCY – LIMITED
  - Dissecting aortic aneurysm
  - Controlled hypotension during surgery

Ganglion Blockers:
Mecamylamine
Trimethaphan

ANTICHOLINERGICS – NEUROMUSCULAR BLOCKERS



- Antinicotinics – decreased binding of acetylcholine to skeletal muscle

- Two types
  - Nondepolarizing & depolarizing
    - Both cause muscle paralysis but depolarizing causes ion channels to open allowing a brief period of muscle contraction.

- Somatic effects
  - Blockade of voluntary & some involuntary muscle contraction
  - DO NOT CAUSE SEDATION. DO NOT PROVIDE RELIEF OF ANXIETY.
  - MUST BE GIVEN RESPIRATORY SUPPORT

ANTICHOLINERGICS – NEUROMUSCULAR BLOCKERS

- When do we use these medications:
  - Surgery
- Non-depolarizing
  - Rocuronium
    - Competitive antagonist at nicotinic receptor
    - Reversed by neostigmine
- Depolarizing
  - Succinylcholine
    - Nicotinic agonist
    - Not metabolized at the synapse, receptor desensitization

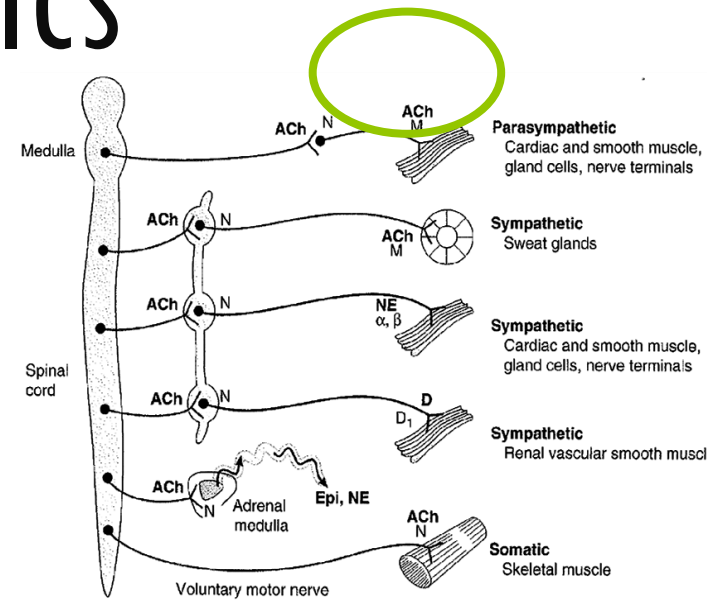
Neuromuscular Blockers:
Succinylcholine
Rocuronium

ANTICHOLINERGICS – NEUROMUSCULAR BLOCKERS

- Why CAN'T neostigmine be used as an antidote for succinylcholine?

ANTICHOLINERGICS – ANTIMUSCARINICS

- Antimuscarinics – Decreased binding of acetylcholine to muscarinic receptors



- Small dose effects
  - Reduced saliva, sweat, and bronchial secretions, increase heart rate, inhibit accommodation

- Large dose effects
  - inhibit micturition, decreased digestive muscle tone, & decreased gastric motility

- Prototype drug - Atropine

ANTICHOLINERGICS – ANTIMUSCARINICS

- Eye
  - Dilation of pupil, relaxation of ciliary muscle
  - Use with care in patients with glaucoma
    - Mechanism for increasing intraocular pressure???
- Even eye drops can cause systemic effects

ANTICHOLINERGICS – ANTIMUSCARINICS

- Skin and mucous membranes
  - Decreased sweating
    - Dry & hot skin
  - Decreased glandular secretions
    - Dry mouth, nose, pharynx, and bronchi
- Respiratory system
  - Decreased secretion – pharynx, nose, and bronchi
  - Relaxation of smooth muscles of airway
    - Breathe more easily

ANTICHOLINERGICS – ANTIMUSCARINICS

- Cardiovascular system effects

- Low dose
  - Slightly slowed heart rate – from depression of the cardiac center in the brain

- High dose
  - Increase in heart rate due to vagal verve blockage, facial redness

ANTICHOLINERGICS – ANTIMUSCARINICS

GI tract

- Little effect on secretions
  - Stomach, intestinal, pancreatic, gallbladder
- Greater effects on food movement
  - Peristalsis, GI tone

Urinary tract

- Muscles of the urinary system
  - Relaxation of detrusor
- Sphincters of the urinary system
  - Constricted
- Relaxation of fundus and ureter

ANTICHOLINERGICS – ANTIMUSCARINICS

Dose response

- Low doses
  - Little to no adverse effect
- High doses
  - Restlessness, wakefulness, talkativeness…leading to delirium, stupor, and coma

CNS conditions

- Parkinson's disease
  - Decreased tremor
- Respiratory depression
  - Increased breath rate and deeper breathing

ANTICHOLINERGICS – ANTIMUSCARINICS

- When do we use these medications?
- Dilate eye
  - Ophthalmic exam
- Motion sickness
  - Central action – depresses vestibular function
- IBS & diarrhea
  - Slow GI motility
  - Can be combined with opioids
- Urinary disorders
  - Decrease urinary leakage and incontinence
- Parkinson's
  - Decrease tremor & oral secretions

Muscarinic antagonists: Scopolomine, benztropine, ipratropium, tiotropium, tolderodine, solifenacin, darfenacin

ANTICHOLINERGICS – ANTIMUSCARINICS

MAD AS A HATTER

DRY AS A BONE

RED AS A BEET

BLIND AS A BAT

QUESTIONS

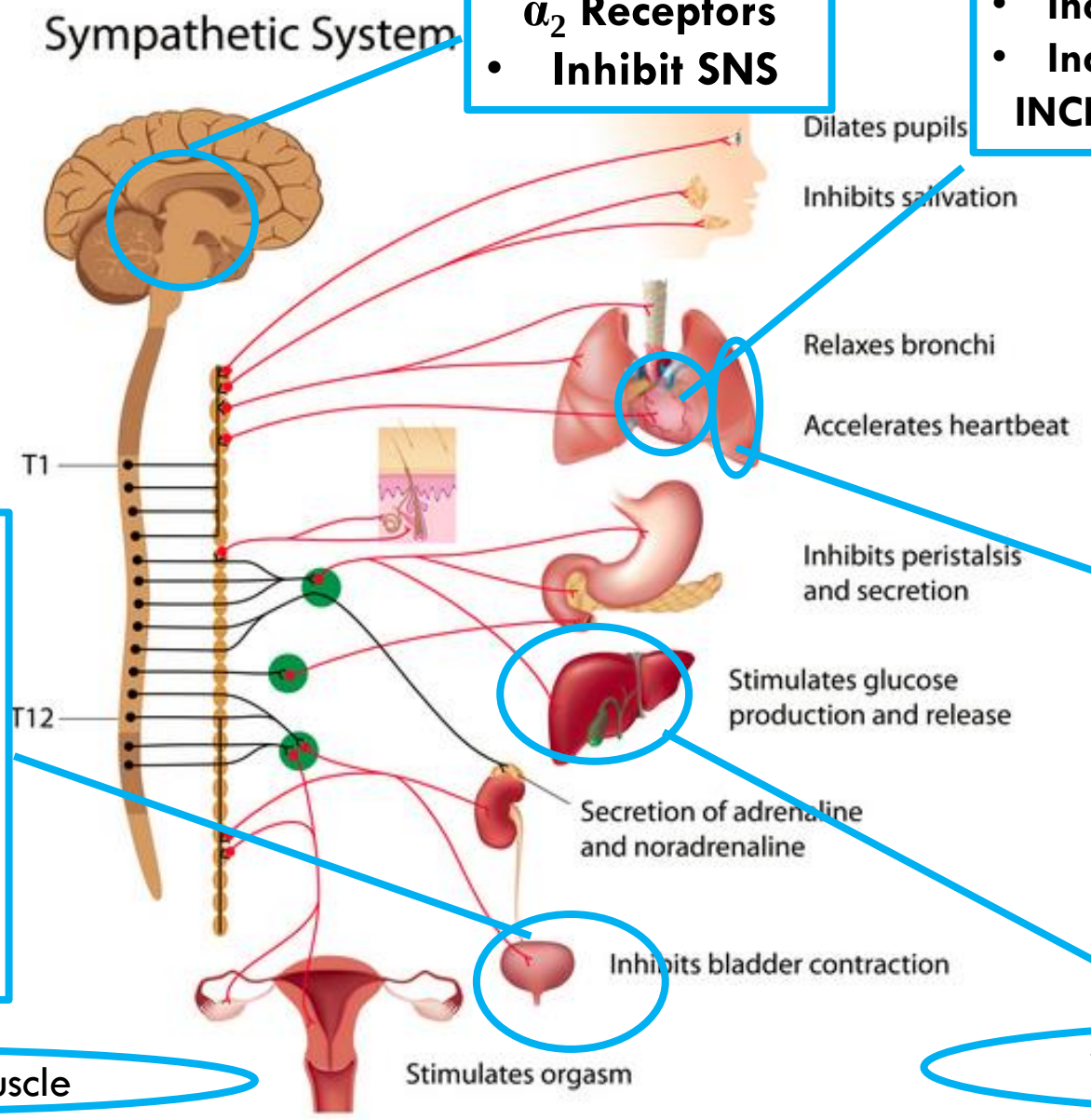
LEARNING OBJECTIVES – ADRENERGIC AGONISTS

- Know the receptor location and neurotransmitter involved in direct acting and indirect acting drugs of the cholinergic agonist class
- Know the physiologic results of the activation or inhibition of those receptors
- Know what substances are considered to be catecholamines
- Understand the differences in binding affinities of the catecholamines and the physiologic results of that
- Know the receptor locations
- Understand shock and the first choice treatment of that condition

SYMPATHETIC NERVOUS SYSTEM

M Receptors

M receptors on the sweat glands = increased sweating



α_2 Receptors

- Inhibit SNS

B_1 Receptor

- Increase HR
- Increase conduction AV node
- Increase force of contraction

INCREASED CARDIAC OUTPUT

B2 Receptors

- Lungs
  - Relaxation of bronchial smooth muscle
- Liver
  - Increased glucose production
    - Gluconeogenesis
    - Glycogenolysis
- Vascular smooth muscle
  - Vasodilation of arteries to skeletal muscle and liver

Vascular smooth muscle

α1 Receptors

- Prostate gland
  - Smooth muscle contraction (urinary obstruction)
- Vascular smooth muscle
  - Most other vessels - contraction

Vascular smooth muscle

SYMPATHETIC NERVOUS SYSTEM

- Neurotransmitters (catecholamines)
  - Epinephrine, Norepinephrine, Dopamine

Dopamine

D
At low doses

Vasodilation of the renal and splanchnic arteries

NO CLINICAL SIGNIFICANCE

B_1
At low-moderate doses

Directly – Increase cardiac contractility
Indirectly – Release NE from storage site in neuron

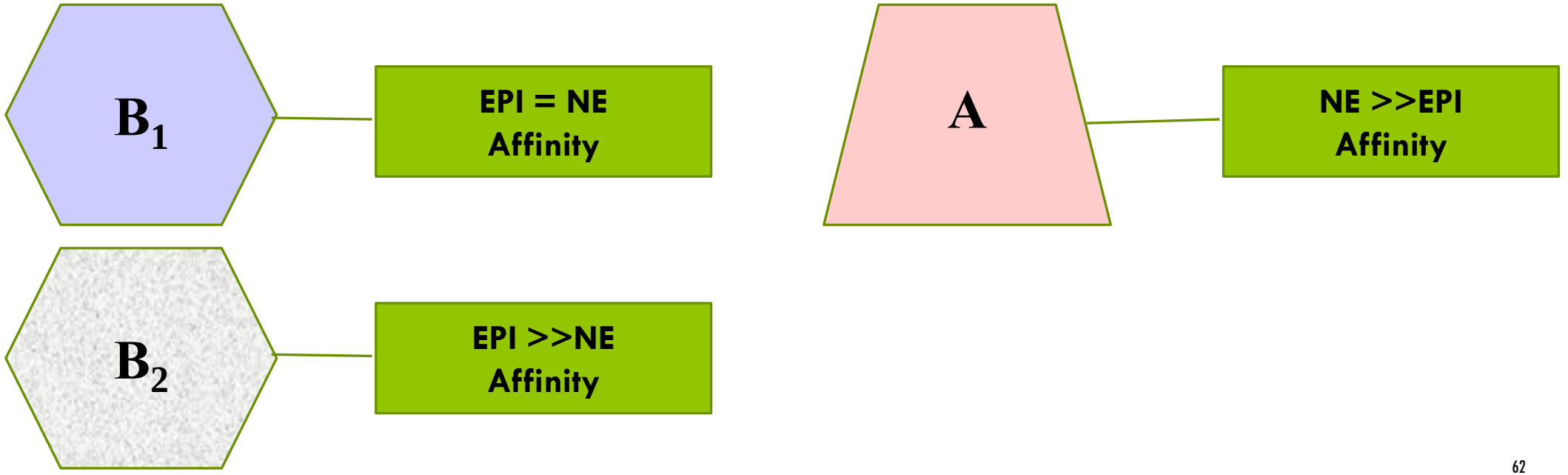
Increase stroke volume and cardiac output/HR mild increase at low doses **DILATION OF RENAL, MESENTERIC, CORONARY, &CEREBRAL BLOOD VESSELS

A
At high doses

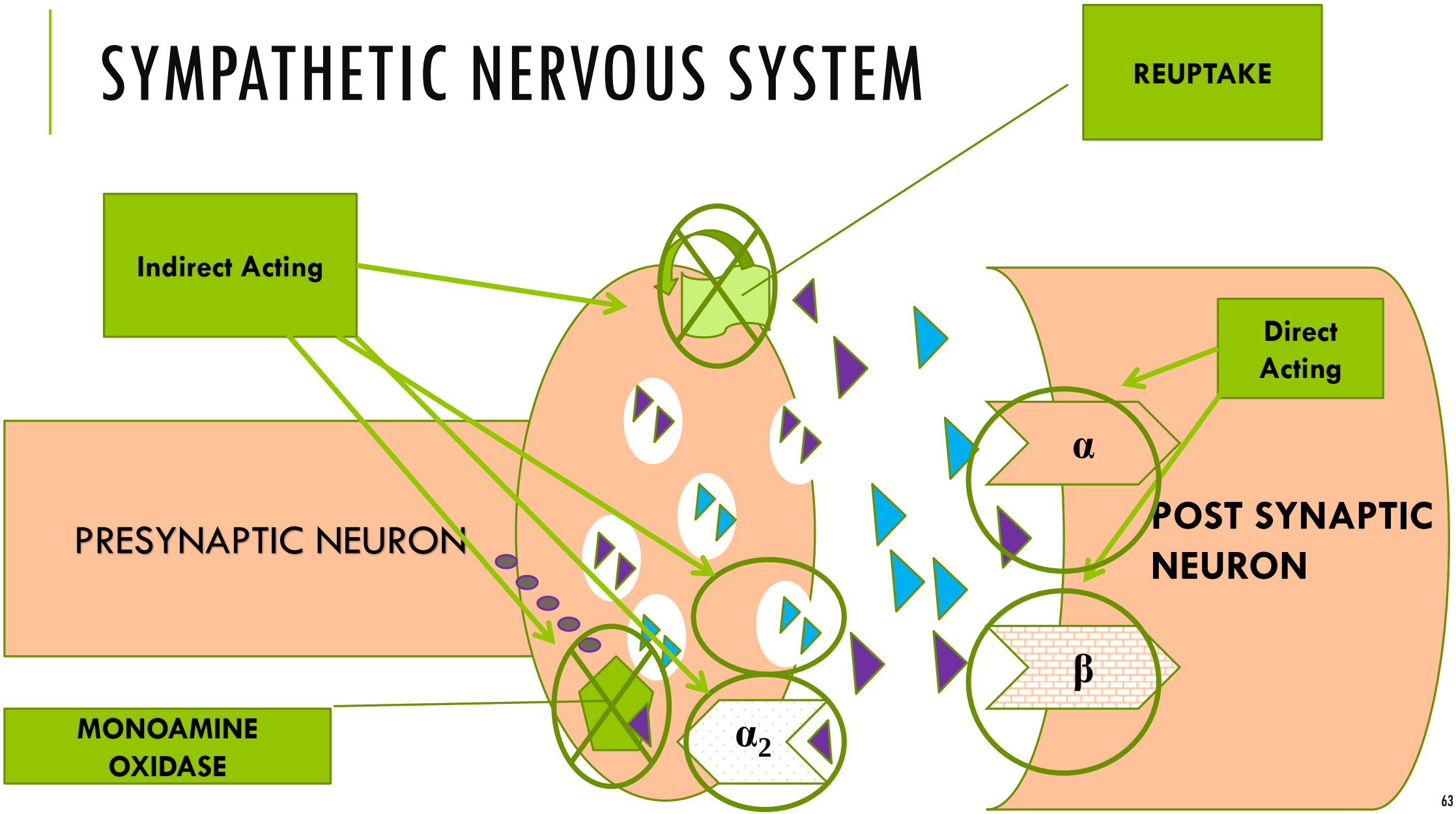
Vasoconstriction and increase in peripheral vascular resistance.
Reduced urinary output

SYMPATHETIC NERVOUS SYSTEM

- Neurotransmitters (catecholamines)
  - Epinephrine, Norepinephrine, Dopamine

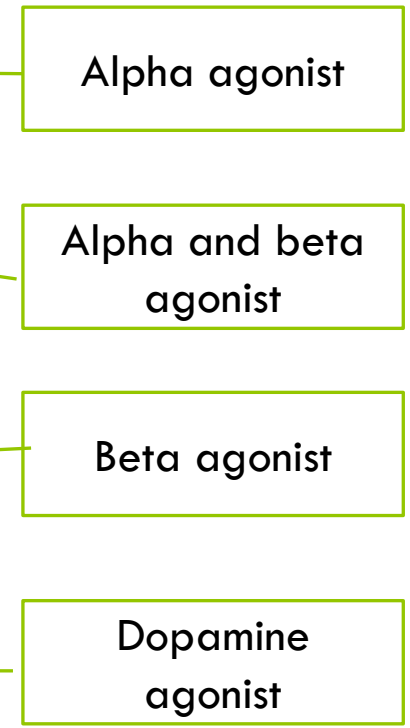


SYMPATHETIC NERVOUS SYSTEM



SYMPATHETIC NERVOUS SYSTEM – DIRECT ACTING AGONISTS

- Medications
  - Clonidine
  - Phenylephrine
  - Norepinephrine
  - Epinephrine
  - Dobutamine
  - Isoproterenol
  - Tertbutaline
  - Albuterol
  - Dopamine



SYMPATHETIC NERVOUS SYSTEM – DIRECT ACTING AGONISTS (ALPHA)

- Clonidine
  - Receptor affinity
    - $\alpha_2 > \alpha_1 >>>>> \beta$
    - Uses: Hypertension, migraine prophylaxis, cancer pain
    - Centrally decreases blood pressure by decreasing sympathetic outflow
    - ADRs: Xerostomia, skin rash, drowsiness

- Phenylephrine
  - Receptor affinity
    - $\alpha_1 > \alpha_2 >>>>> \beta$
    - Can be used to raise blood pressure – REFLEX DECREASE IN HEART RATE, primary use as a decongestant or used to dilate pupils
    - ADRs: Nasal burning and discharge – local effects

SYMPATHETIC NERVOUS SYSTEM – DIRECT ACTING AGONISTS (ALPHA & BETA)

- Epinephrine & Norepinephrine
  - Epinephrine agonist of all 3 receptors
    - Modest change in blood pressure
  - **Norepinephrine = low affinity towards beta 2**
    - Large increase in blood pressure

- Epi, NE, & Dopamine – DO NOT CROSS BBB

A_1
Vasoconstriction = Increased blood pressure

B_2
Vasodilation = Decreased blood pressure

B_1
Increased cardiac output (increased contractility &rate) = Increased blood pressure

SYMPATHETIC NERVOUS SYSTEM – DIRECT ACTING AGONISTS (ALPHA & BETA)

Epinephrine

Uses: Allergic reaction, hypotension/shock, pupil dilation during eye surgery

ADRs: Arrhythmia, anxiety, dry throat, urinary retention

Norepinephrine

Uses: First choice vasopressor in treatment of sepsis an septic shock, severe hypotension after fluid replacement

ADRs: Arrhythmia, anxiety, and difficulty breathing

*Levophed

SYMPATHETIC NERVOUS SYSTEM – DIRECT ACTING AGONISTS (ALPHA & BETA)

Why is NE the first choice in the treatment of septic shock?

SYMPATHETIC NERVOUS SYSTEM – DIRECT ACTING AGONISTS (BETA AGONISTS)

Isoproterenol

$\beta_1 = \beta_2 >>>>> \alpha$

- Non-selective beta agonist
- Potent cardiac stimulant, increases cardiac output
- Vasodilator, decreases arterial pressure
- Causes bronchodilation
- Uses: Bronchospasm associated with asthma, emphysema, and bronchitis
- ADRs: Arrhythmia, anxiety, red tinged saliva

Tertbutaline

$\beta_2 > \beta_1 >>>> \alpha$

- Selective beta-2 agonists
- Cause bronchodilation
- Relaxes uterine wall
- Uses: Bronchoconstriction, premature labor
- ADRs: Increased heart rate, nervousness, trembling, headache, dry mouth

SYMPATHETIC NERVOUS SYSTEM – DIRECT ACTING AGONISTS (BETA AGONISTS)

Dobutamine

$\beta_1 > \beta_2 >>>> \alpha$

- Selective beta-1 agonist
- Cardiac stimulant
- Uses: Cardiac decompensation (heart failure), sepsis
- ADRs: Chest pain, palpitations, PVCs, headache, nausea

Albuterol

$\beta_2 > \beta_1 >>>> \alpha$

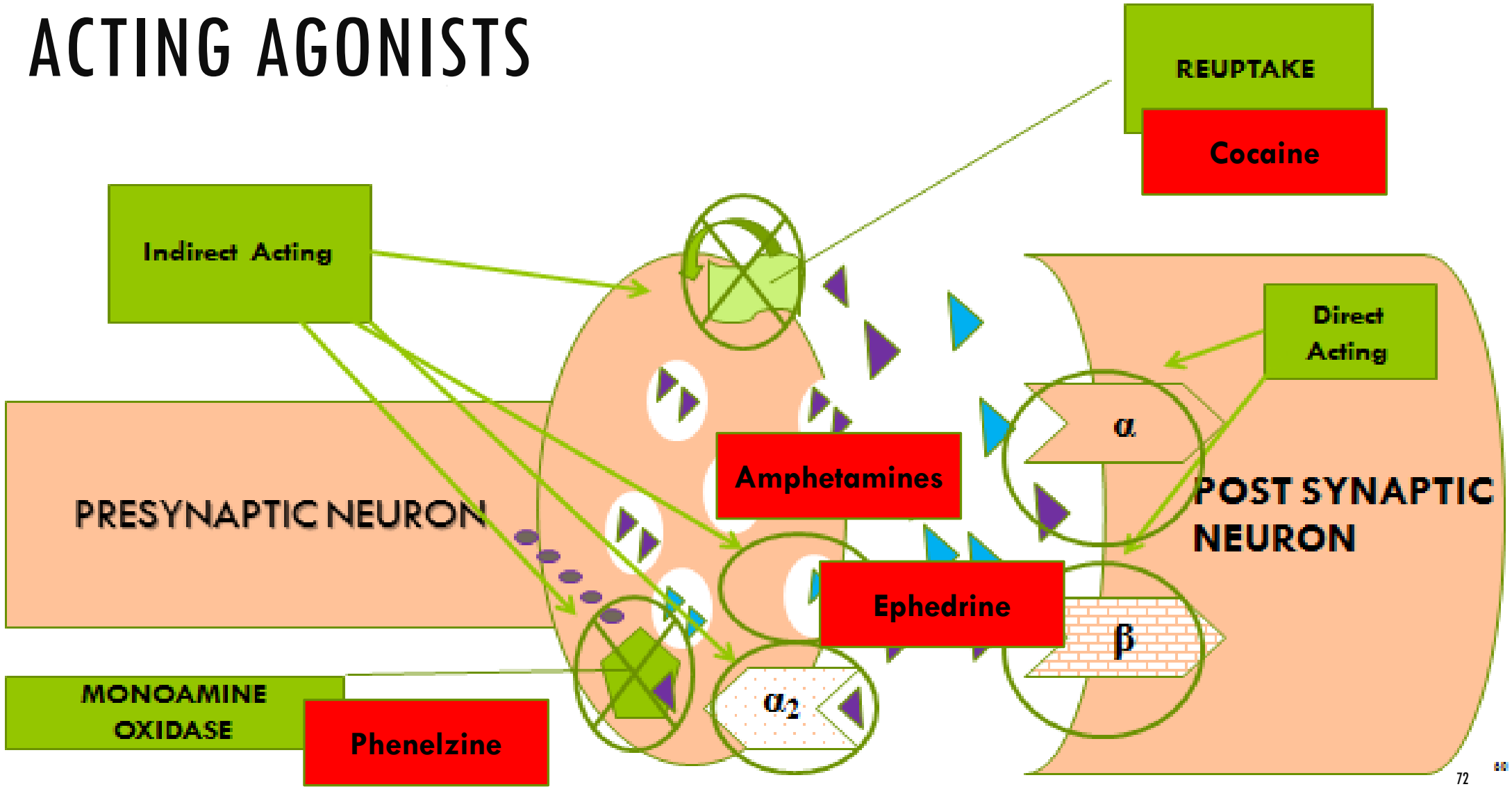
- Selective beta-2 agonists
- Cause bronchodilation
- Uses: Bronchospasm in asthma & COPD & hyperkalemia
- ADRs: Tachycardia, excitement, nervousness, tremor

SYMPATHETIC NERVOUS SYSTEM – DIRECT ACTING AGONISTS (DOPAMINE AGONISTS)

Dopamine $D_1 = D_2 >> \beta_1 >> \alpha_1$

- Vasoconstriction and increase in peripheral vascular resistance.
- Reduced urinary output
- Vasodilation of the renal and splanchnic arteries
- Directly – Increase cardiac contractility (beta 1)
- Indirectly – Release NE from storage site in neuron (beta 1)
- Increase stroke volume and cardiac output/HR mild increase at low doses **DILATION OF RENAL, MESENTERIC, CORONARY, &CEREBRAL BLOOD VESSELS (alpha 1)
- Uses: Adjunct in the treatment of shock & facilitate diuresis and preserve renal function
- ADRs: Chest pain, arrhythmia, anxiety, headache, nausea, vomiting

SYMPATHETIC NERVOUS SYSTEM – INDIRECT ACTING AGONISTS



SYMPATHETIC NERVOUS SYSTEM – INDIRECT ACTING AGONISTS – RELEASING AGENTS

Amphetamine, methamphetamine, methylphenidate

- Elevates mood and alertness
- Decreased appetite
- Uses: Amphetamine & methamphetamine
  - Drugs of abuse
- Uses: Methylphenidate
  - ADHD – potential for abuse

- ADRs: Addiction, tachycardia, blurred vision, headache, insomnia, skin rash, weight loss, dry mouth

- Lipophilic and can penetrate the BBB

SYMPATHETIC NERVOUS SYSTEM – INDIRECT ACTING AGONISTS – RELEASING AGENTS & DIRECT BINDING

Ephedrine

- Plant derived and has mild stimulant effect
- Long duration of action
- Non selective
- Uses: Primarily as a nasal decongestant, but also stress incontinence in women and pressor effects
- ADRs: Hypertension, tachycardia, nausea and vomiting, tremor, and anxiety

- ****pseudoephedrine – indirect action only but still a nasal decongestant and can reduce stress incontinence in women

SYMPATHETIC NERVOUS SYSTEM – INDIRECT ACTING AGONISTS – REUPTAKE AND MAOI$_S$

Cocaine

Local anesthetic properties/major drug of abuse

- Inhibits the reuptake of catecholamine at the cleft
- CNS effect substantial

Phenelzine

Monoamine oxidase inhibitor and increases storage supply of norepinephrine in CNS

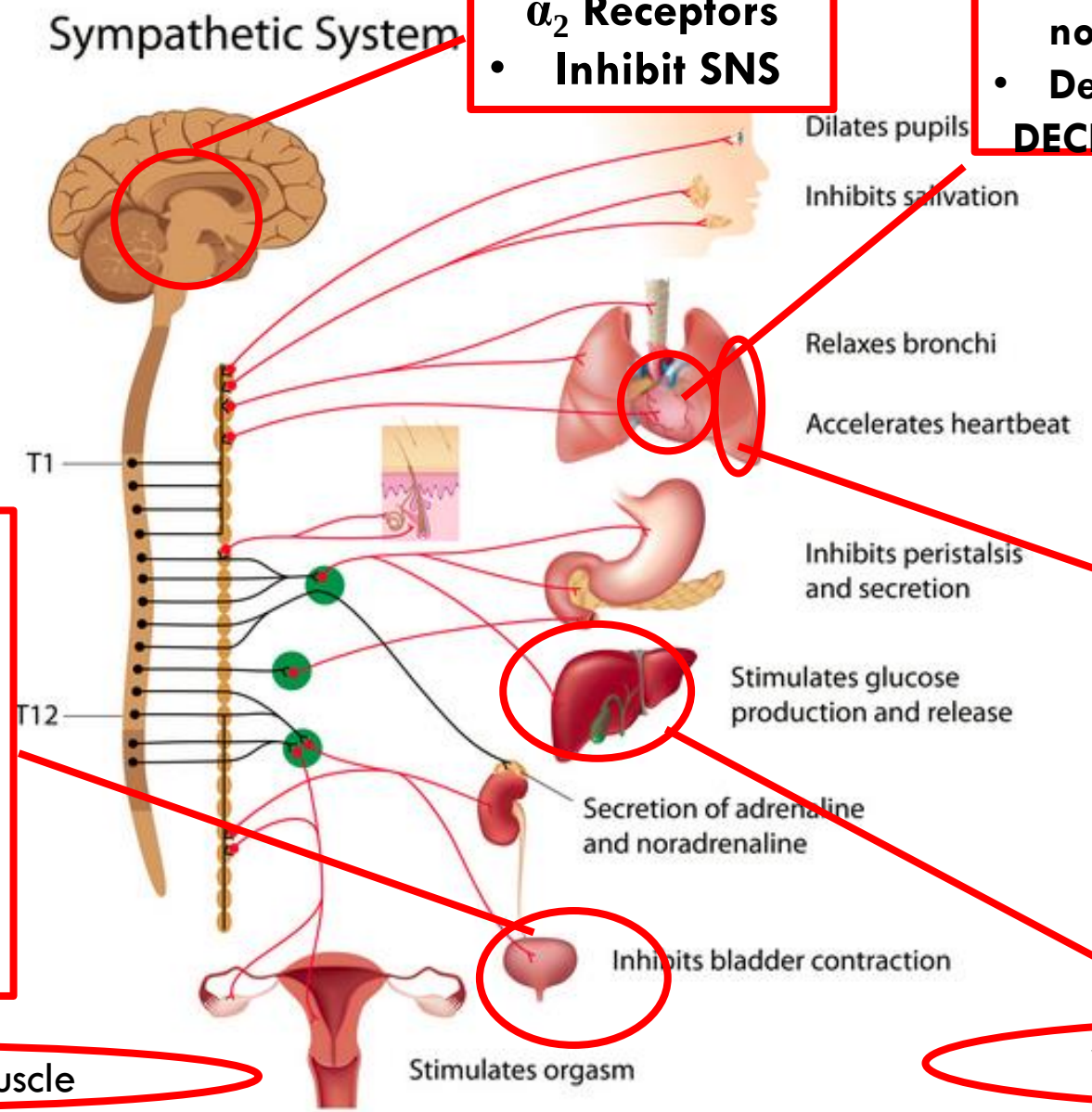
- Uses: Depression, bulemia
- ADRs: Orthostatic hypotension, headache, xerostomia, weight gain, sexual dysfunction
- Tyramine foods – dangerous hypertension
  - Pickled, cured meats, beer, aged cheese

QUESTIONS

LEARNING OBJECTIVES – ADRENERGIC ANTAGONISTS

- Know the receptor location and neurotransmitter involved in direct acting and indirect acting drugs of the cholinergic agonist class
- Know the physiologic results of the activation or inhibition of those receptors
- Know the receptor locations
- Know the physiologic results of administering a selective agent over a non-selective agent
- Understand why certain agents within a drug class might be used for a particular indication and the reasons for the selection of that medication
- Understand reflex tachycardia

SYMPATHETIC NERVOUS SYSTEM



α_2 Receptors
- Inhibit SNS

B_1 Receptor
- Decreased HR
- Decreased conduction AV node
- Decreased force of contraction

DECREASED CARDIAC OUTPUT

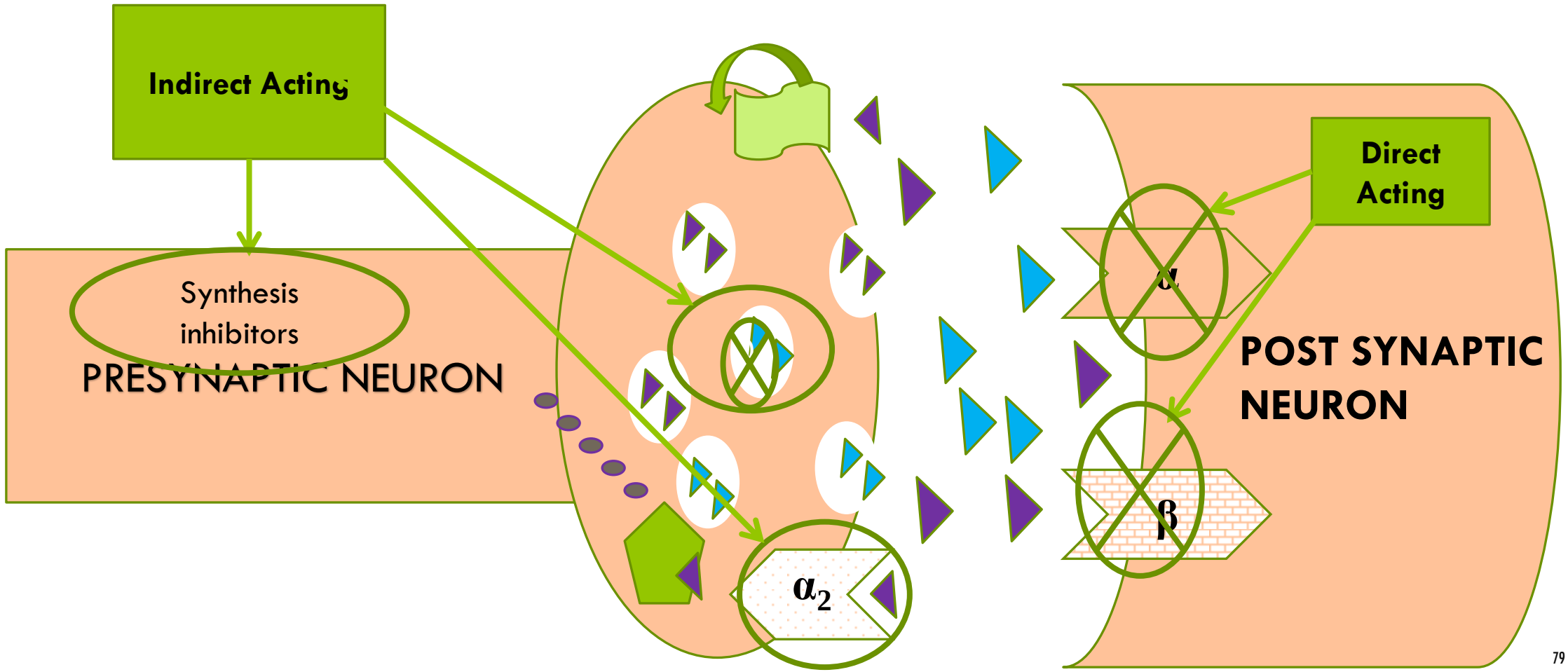
B2 Receptors
- Lungs
  - Contraction of bronchial smooth muscle
- Liver
  - Decreased glucose production
- Vascular smooth muscle
  - Vasoconstriction of arteries to skeletal muscle and liver

Vascular smooth muscle

α1 Receptors
- Prostate gland
  - Smooth muscle relaxation(urinary obstruction)
- Vascular smooth muscle
  - Most other vessels - relaxation

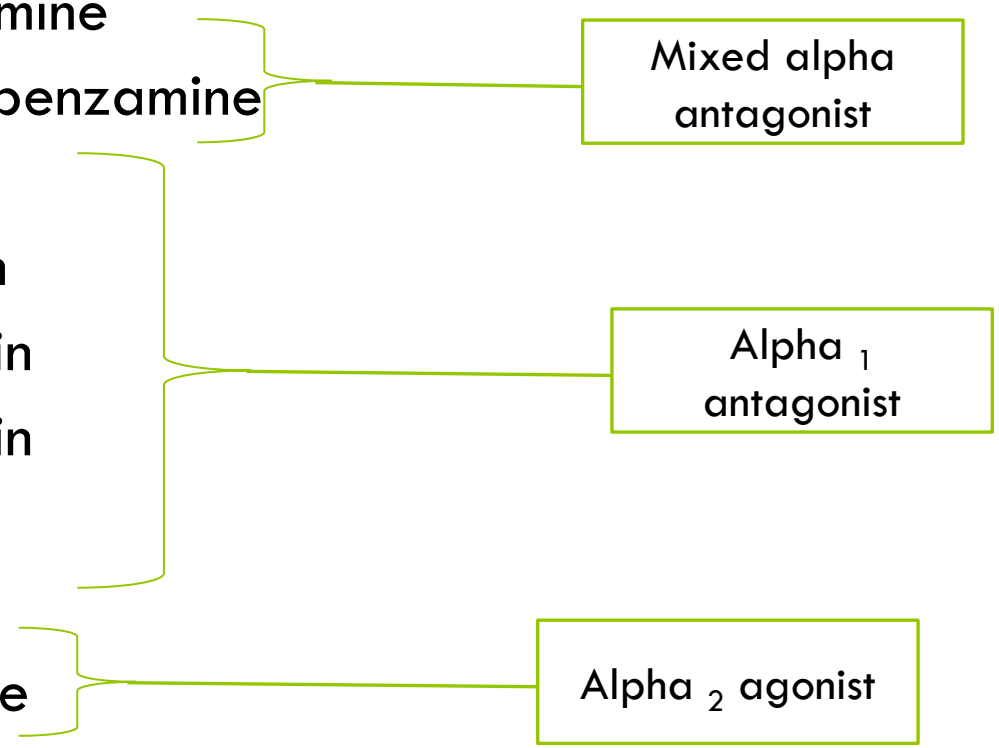
Vascular smooth muscle

SYMPATHETIC NERVOUS SYSTEM – ADRENERGIC ANTAGONISTS



SYMPATHETIC NERVOUS SYSTEM – DIRECT ACTING ANTAGONISTS

- Medications
  - Phentolamine
  - Phenoxybenzamine
  - Prazosin
  - Terazosin
  - Doxazosin
  - Tamsulosin
  - Alfuzosin
  - Yohimbine



SYMPATHETIC NERVOUS SYSTEM – MIXED ALPHA ANTAGONISTS

Phentolamine

- $\alpha_1 = \alpha_2$
- Very non-selective and can even bind to muscarinic, H1, and H2 receptors.
- α_1 - blocked, causing vasoconstriction
- α_2 - blocked, allowing the continued release of catecholamine to bind beta 1
- Baroreflex
- Poor oral absorption
- Uses: Pheochromocytoma & erectile dysfunction
- ADRs: Tachycardia, arrhythmia, MI, GI stimulation (diarrhea & increased gastric acid)

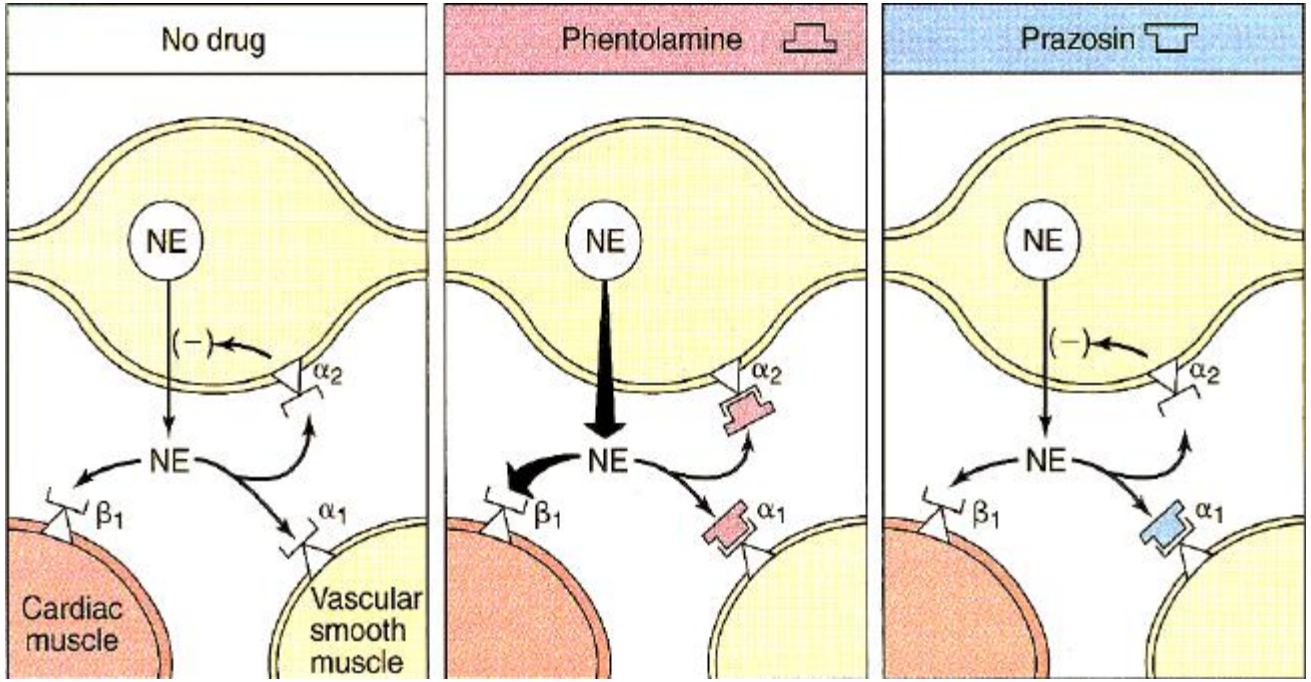
SYMPATHETIC NERVOUS SYSTEM – MIXED ALPHA ANTAGONISTS

Phenoxybenzamine

$\alpha_2 > \alpha_1$

- Blocks alpha 1 & 2 as well as receptors of acetylcholine, H1, and serotonin receptors
- Decreases blood pressure – especially when HTN caused by increased SNS tone
- Baroreflex and some alpha 2 blockade = potential increase in cardiac output

- Uses: Pheochromocytoma, and surgery prep
- ADRs: Postural hypotension, tachycardia, stuffy nose, sexual dysfunction, CNS – fatigue, nausea, sedation



SYMPATHETIC NERVOUS SYSTEM – ALPHA 1 ANTAGONISTS

Prazosin, doxazosin, tamsulosin, terazosin, alfuzosin

- Uses: BPH & moderate hypertension
- Alpha 1 >>>>>> alpha 2
- All generally work by blocking alpha 1 receptors in the smooth muscle arteries, veins, and prostate. However, there are some differences within the class
- ADRs: Postural hypotension, reflex tachycardia, retention of fluid and salt, sexual dysfunction

SYMPATHETIC NERVOUS SYSTEM – ALPHA 1 ANTAGONISTS

Prazosin

Use: Hypertension & PTSD

- May increase HDL and decrease LDL

Tamsulosin

Use: BPH, chronic urinary obstruction

- Little effect on BP
- Useful in patients who may have experienced postural hypotension with other alpha 1 blockers
- Greater selectivity for alpha 1a vs alpha 1 b (alpha 1 a most important for prostate)

SYMPATHETIC NERVOUS SYSTEM – ALPHA 2 ANTAGONISTS

Yohimbine

Uses: Reverse sedation in dogs and deer

Other uses: Hallucinogen, aphrodisiac, erectile dysfunction, and reduced libido in women

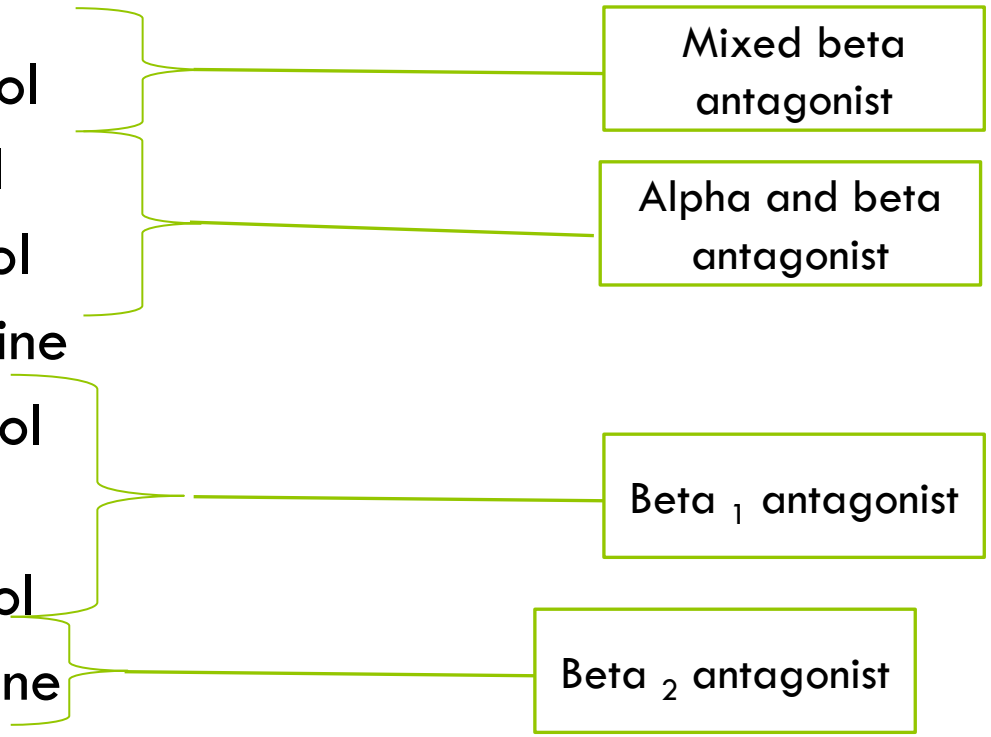
MOA: Centrally acing alpha 2 antagonist to increase sympathetic outflow

ADRs: Nausea/vomiting, tachycardia, anxiety, agitation, tremor, sweat, renal failure, arrhythmia, seizure…

No known antidote but benzodiazepines may help in toxicities associated with agitation, hypertension, and tachycardia

SYMPATHETIC NERVOUS SYSTEM – DIRECT ACTING ANTAGONISTS – BETA ANTAGONISTS

- Medications
  - Pindolol
  - Propanolol
  - Labetalol
  - Carvedilol
  - Dobutamine
  - Metoprolol
  - Atenolol
  - Acebutalol
  - Butaxamine



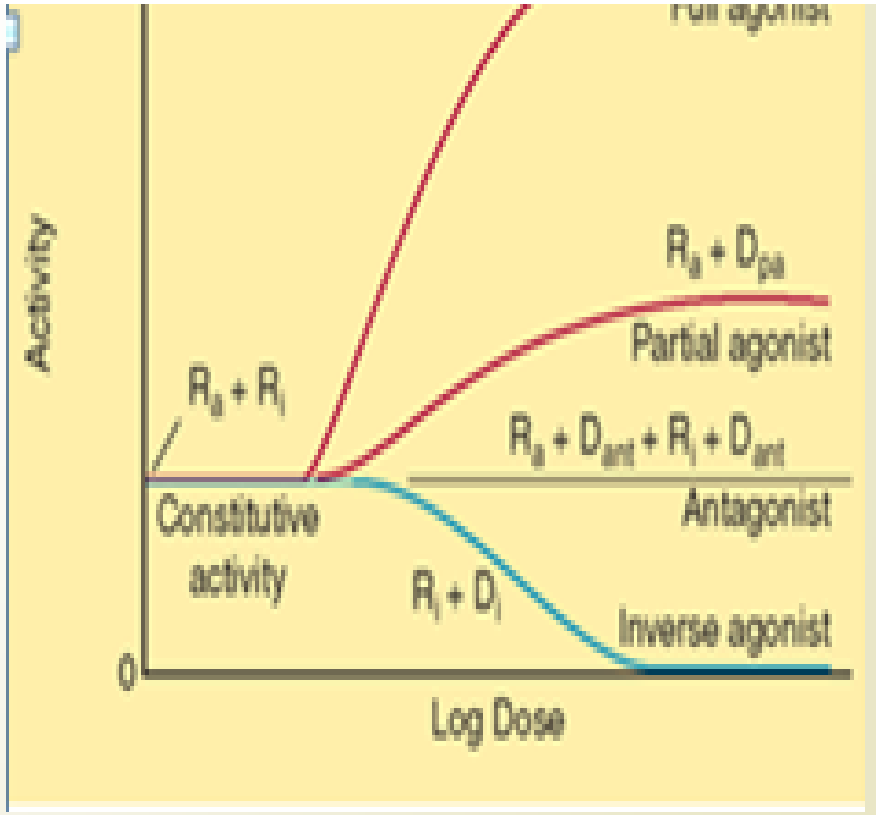
SYMPATHETIC NERVOUS SYSTEM – BETA ANTAGONISTS

Pure Antagonists
- Atenolol
- Carveliolol
- Propranolol

Partial Agonists (ISA)
- Acebutolol
- Labetalol
- Pindolol

Inverse agonists
- Metoprolol
- Bisoprolol

- Partial agonist
  - Exerts less than full receptor effects
  - Active state >Inactive state
- Inverse agonist
  - Less activity than when receptor not being acted on by substance (constitutive activity)
  - Inactive state > active state



SYMPATHETIC NERVOUS SYSTEM – BETA ANTAGONISTS

IN GENERAL: Decrease in blood pressure, cardiac output (decrease in heart rate and contractility, lower blood pressure without creating hypotension

- Most are lipophilic, large Vd, well absorbed
- Some cross the BBB
- Some are metabolized in the liver and some are excreted in the urine as unchanged drug
- Upon administration – rise in PVR, overtime (chronic use) decrease in PVR
- Blockade of beta 2
  - Bronchoconstriction
  - Decreased lipolysis
  - Decreased blood glucose
- ADRs:
  - Sedation, sleep disturbances, depression, bronchospasm
- Taper

SYMPATHETIC NERVOUS SYSTEM – BETA ANTAGONISTS

Propranolol

- Non-selective
- Very lipophilic
- Uses: Hypertension, coronary artery disease, migraine prophylaxis, performance anxiety
  - Can cross the BBB
  - Extensive first pass metabolism (CYP 2D6 & 1A2)
  - Local anesthetic properties
  - May also be used for hyperthyroidism (thyroid storm – excessive catecholamine action on the heart)

SYMPATHETIC NERVOUS SYSTEM – BETA ANTAGONISTS

Metoprolol

- Inverse Agonist
- Moderately lipophilic
- Extensive first pass effect (CYP2D6)
- Local anesthetic
- First choice BB in heart failure

Nadolol

- Pure Antagonist
- Not metabolized
  - Longest half life
    - May increase with kidney disease

SYMPATHETIC NERVOUS SYSTEM – BETA ANTAGONISTS

Labetalol

Hypertension in pregnancy

- Has ISA – less risk for bradycardia (reduced sympathetic response)

NOT TO BE USED IN ACUTE CONGESTIVE HEART FAILURE

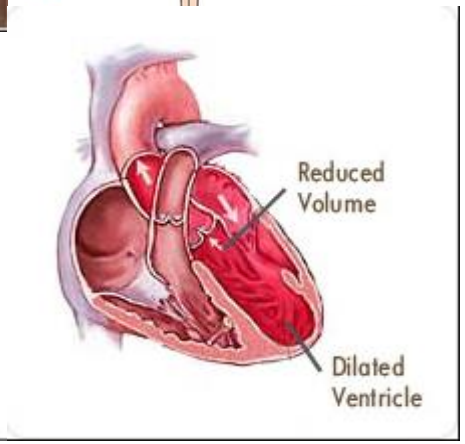
Timolol / Betaxolol

Glaucoma

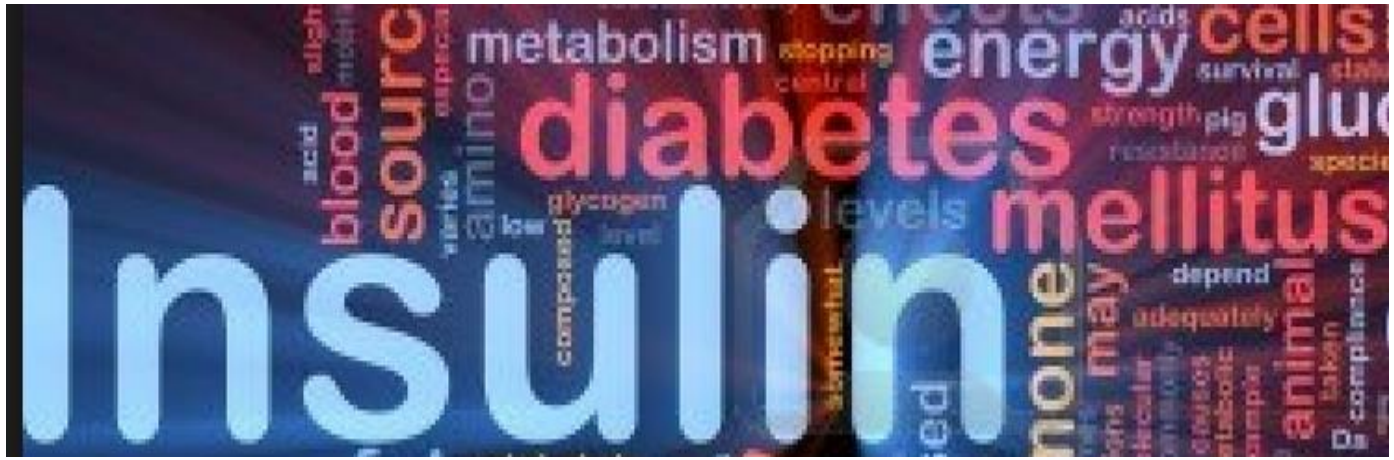
- Reduction in aqueous humor by ciliary body
  - Decreased production

- Timolol – non-selective
  - Bronchospasm
- Betaxolol – selective
  - First choice

SYMPATHETIC NERVOUS SYSTEM – BETA ANTAGONISTS - CONSIDERATIONS



SYMPATHETIC NERVOUS SYSTEM – BETA ANTAGONISTS – MORE CONSIDERATIONS



QUESTIONS