Autonomic Pharmacology

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http://veltman.org/education/autonomic-pharmacology/

Outline
Sympathetic Nervous System

Anatomy and physiology of SNS

Pharmacological effects

Clinical application

Side effects

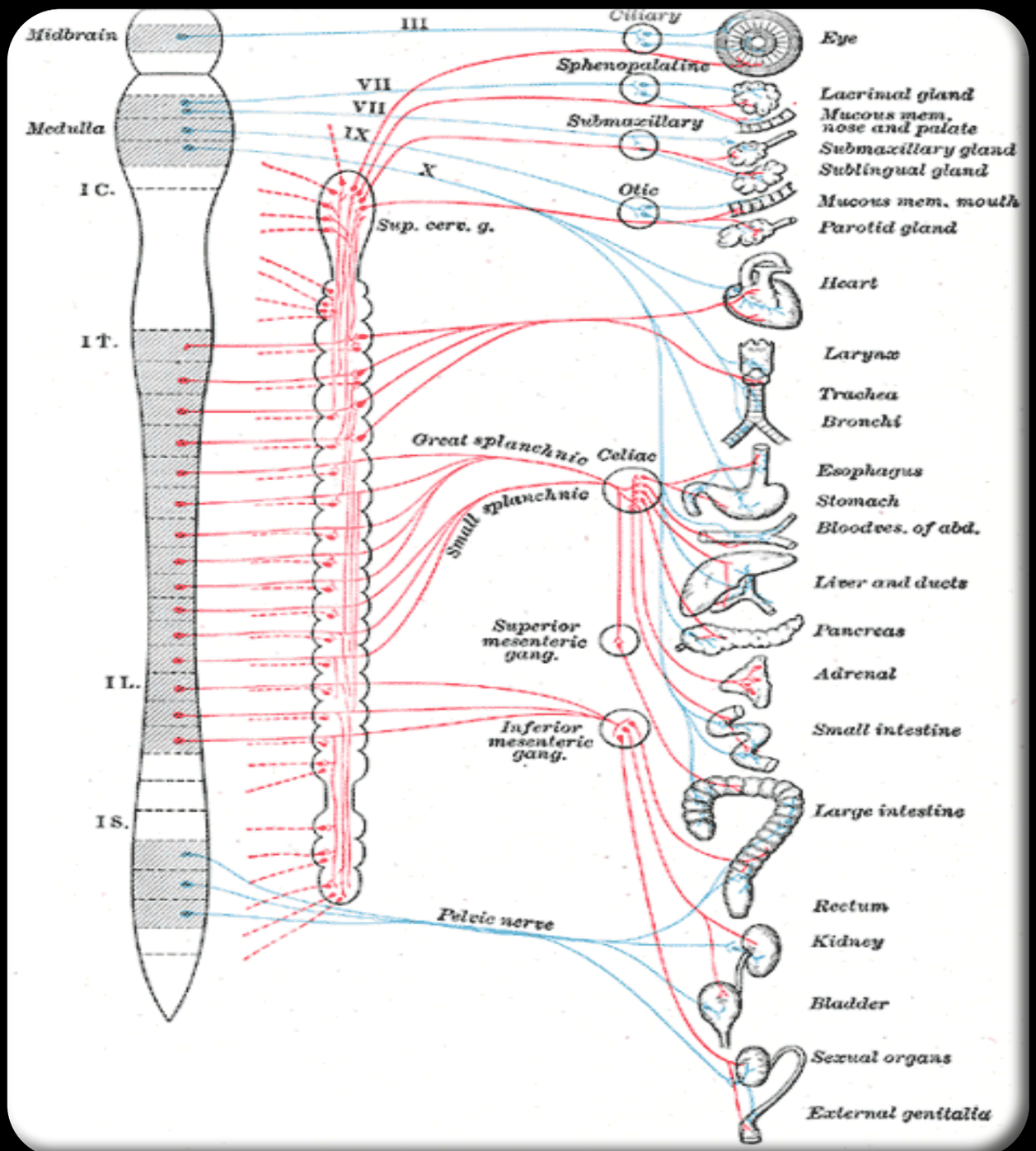
Learning Objectives

Sympathetic Nervous System

- Sympathetic receptors - what they are and do
- Physiological effects of the SNS
- Pharmacological agonists
- Pharmacological antagonists

Sympathetic Nervous System

How does the autonomic nervous system work?



Sensors in body eg:

- Blood pressure
- Osmotic pressure

Message to brainstem

Modulated response via

- Sympathetic nervous system
- Parasympathetic nervous system

Catecholamines

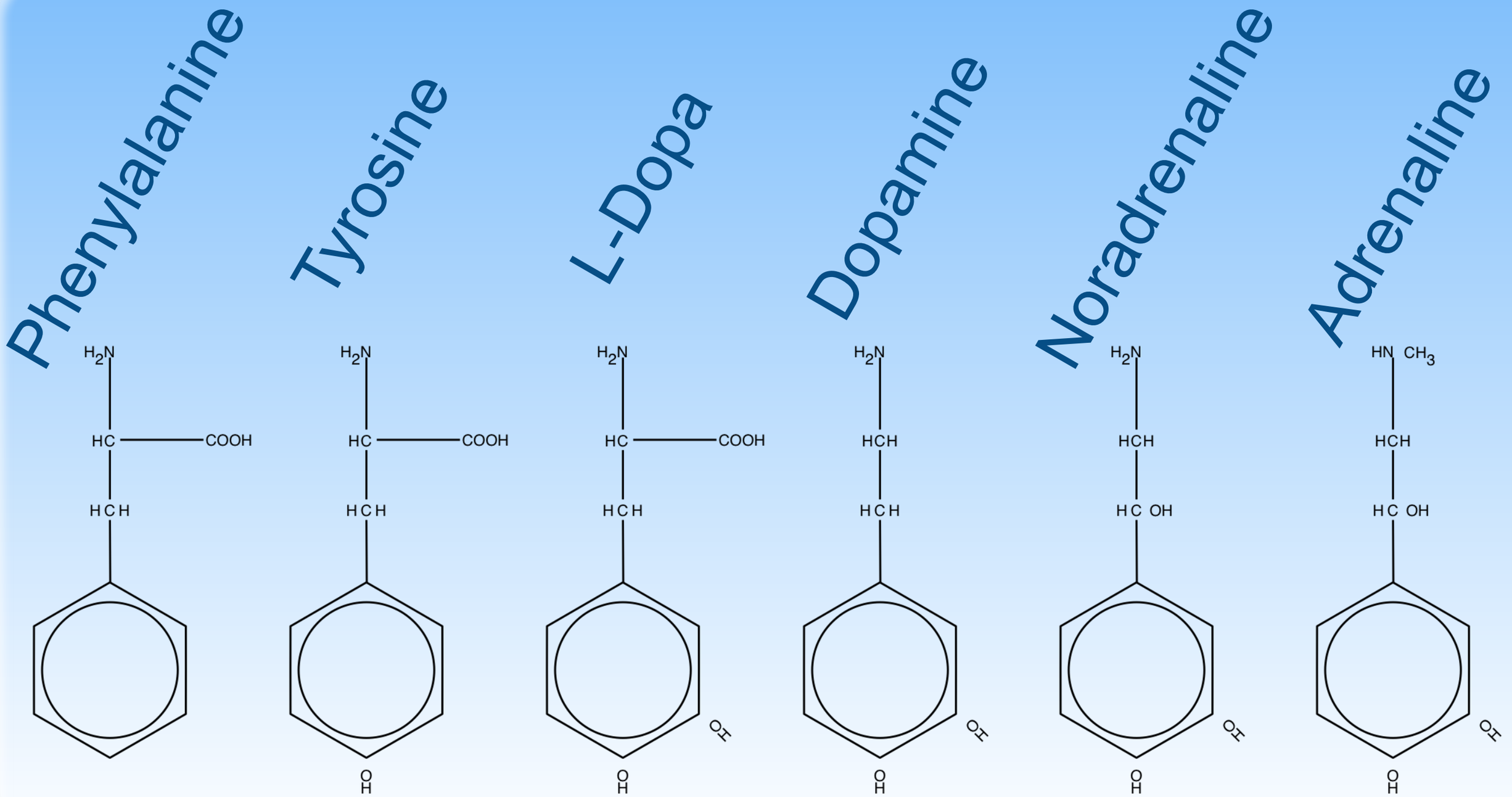
Messengers of the sympathetic nervous system

- Synthesised from amino acids (Tyrosine)

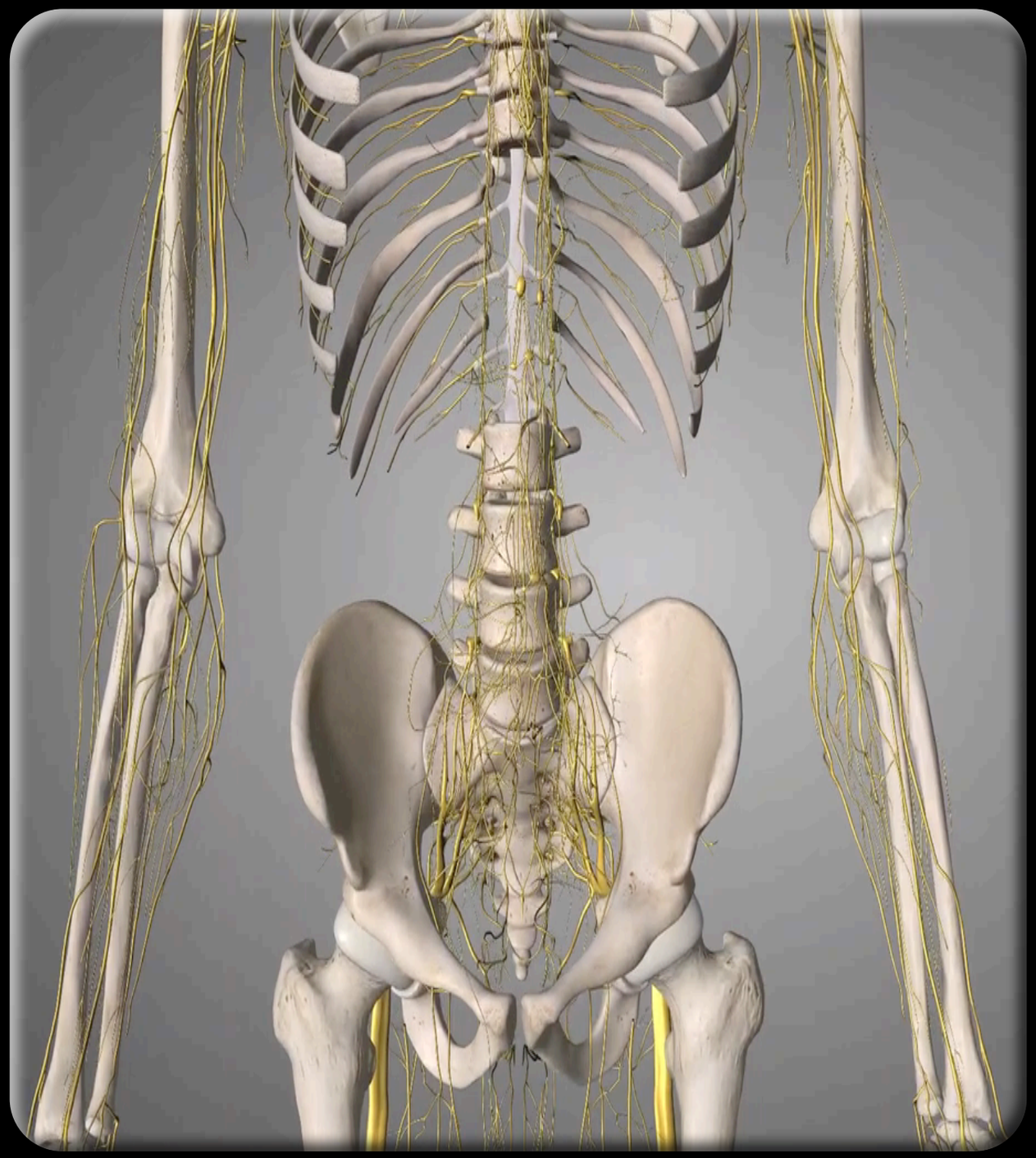
Released from nerve endings

- Have different effects depending on the receptors in that system

Catecholamine Biosynthesis



What is a ganglion?



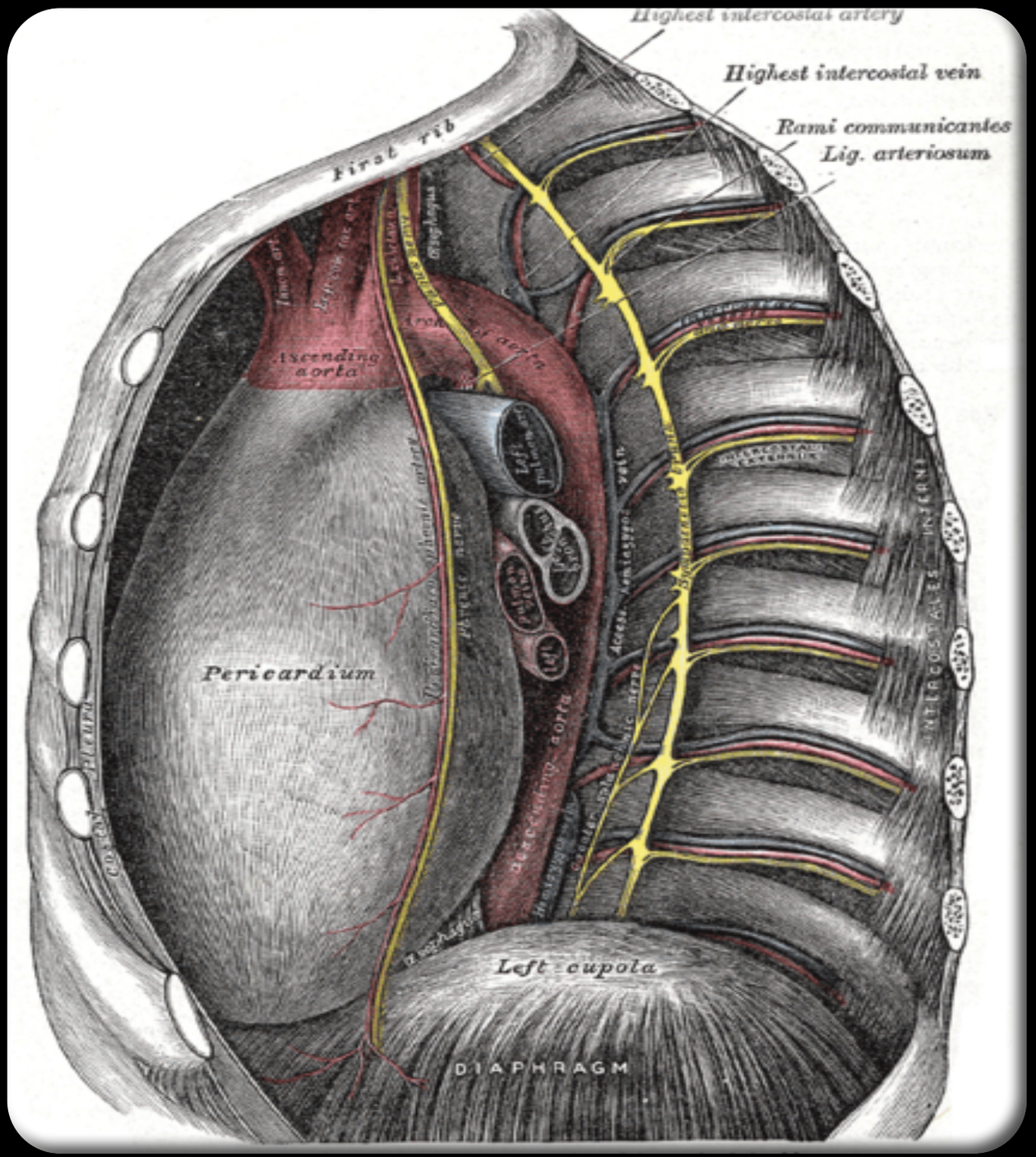
A ganglion is a cluster of nerves

Tens of thousands of nerve cell bodies

This is where the central nervous system sympathetic outflow nerves end.

Synaptic transmission occurs here

Anatomy

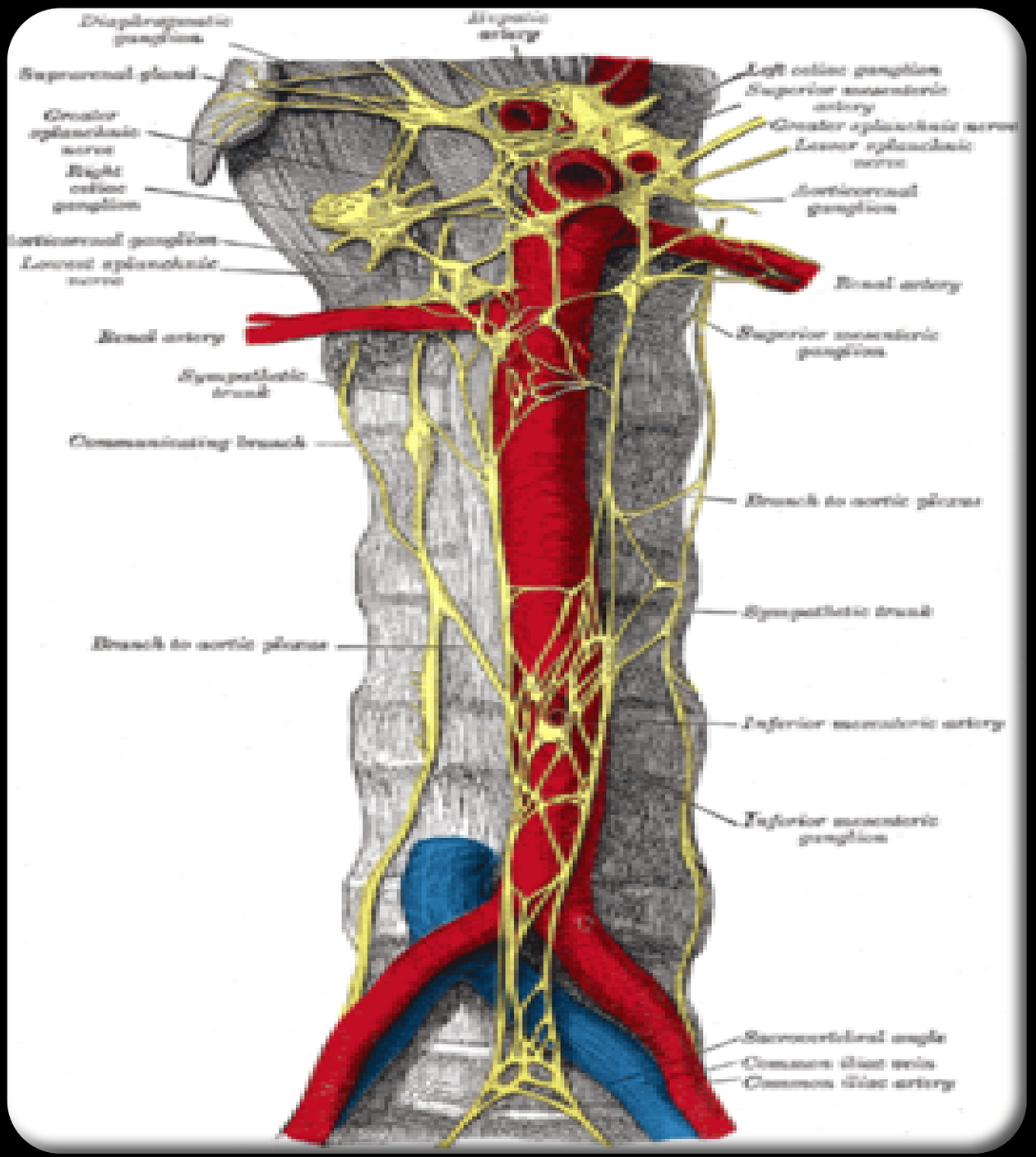


All sympathetic outflow comes from T1-L3

Primary fibres end in the ganglionic junctions

Ganglions cover cervical to sacral regions

Ganglia



Cervical

3 Ganglia

Thoracic

12 Ganglia

Lumbar

4 Ganglia

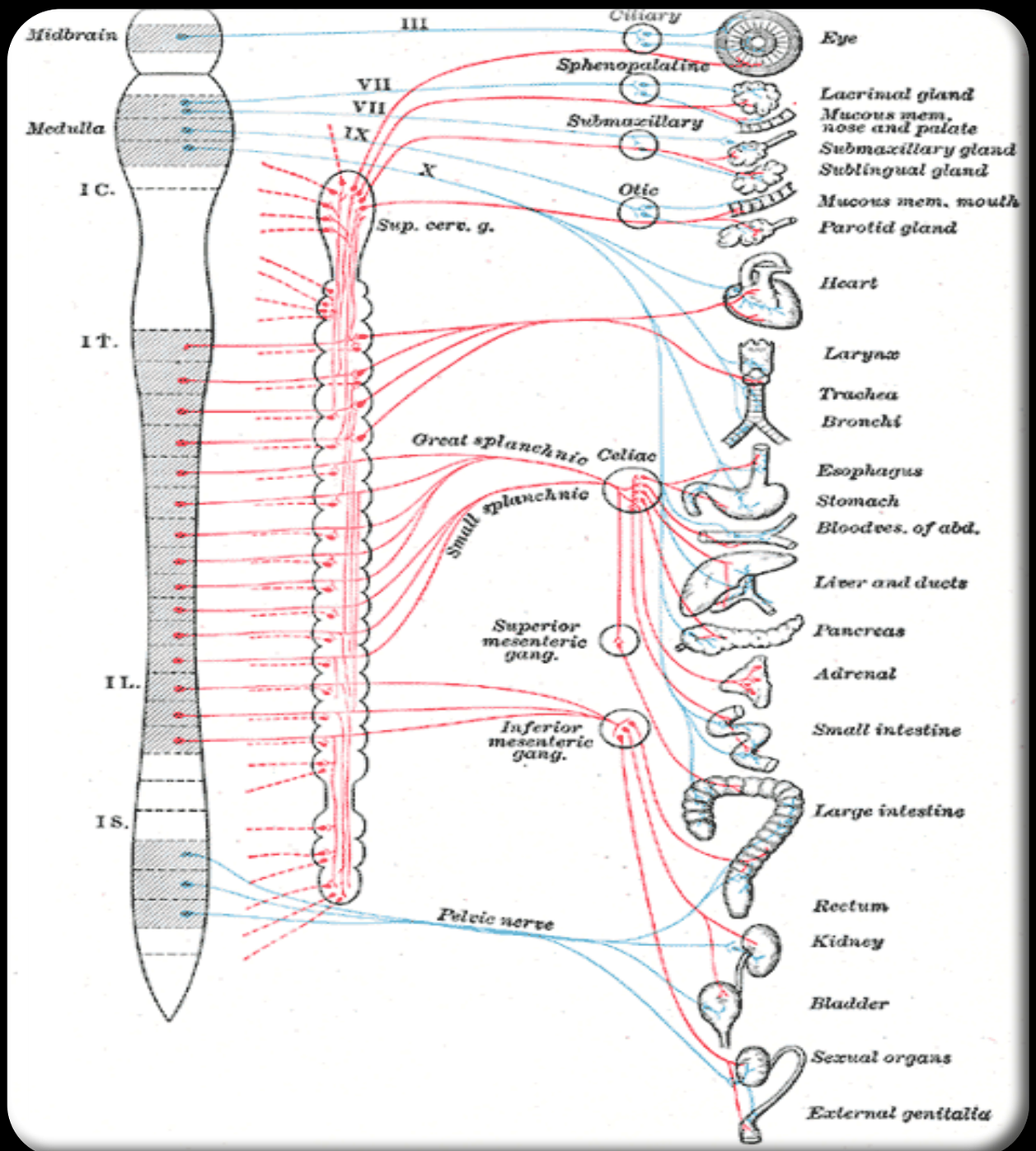
Sacral

4-5 Ganglia

Autonomic Nerves

	Function	Diameter µm	Velocity m/s
A-α	Proprioception, Motor	12-20	70-120
A-β	Touch, Pressure, Motor	5-12	30-70
A-γ	Muscle Spindles	3-6	15-30
A-δ	Pain, Cold, Touch	2-5	12-30
B	Preganglionic	<3	3-15
C-Dorsal Root	Pain, Temp, Reflex	0.4-1.2	0.5-2.0
C-Symp Post	Postganglionic	0.3-1.3	0.7-2.3

How does the autonomic nervous system work?



Sensors in body eg:

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- Osmotic pressure

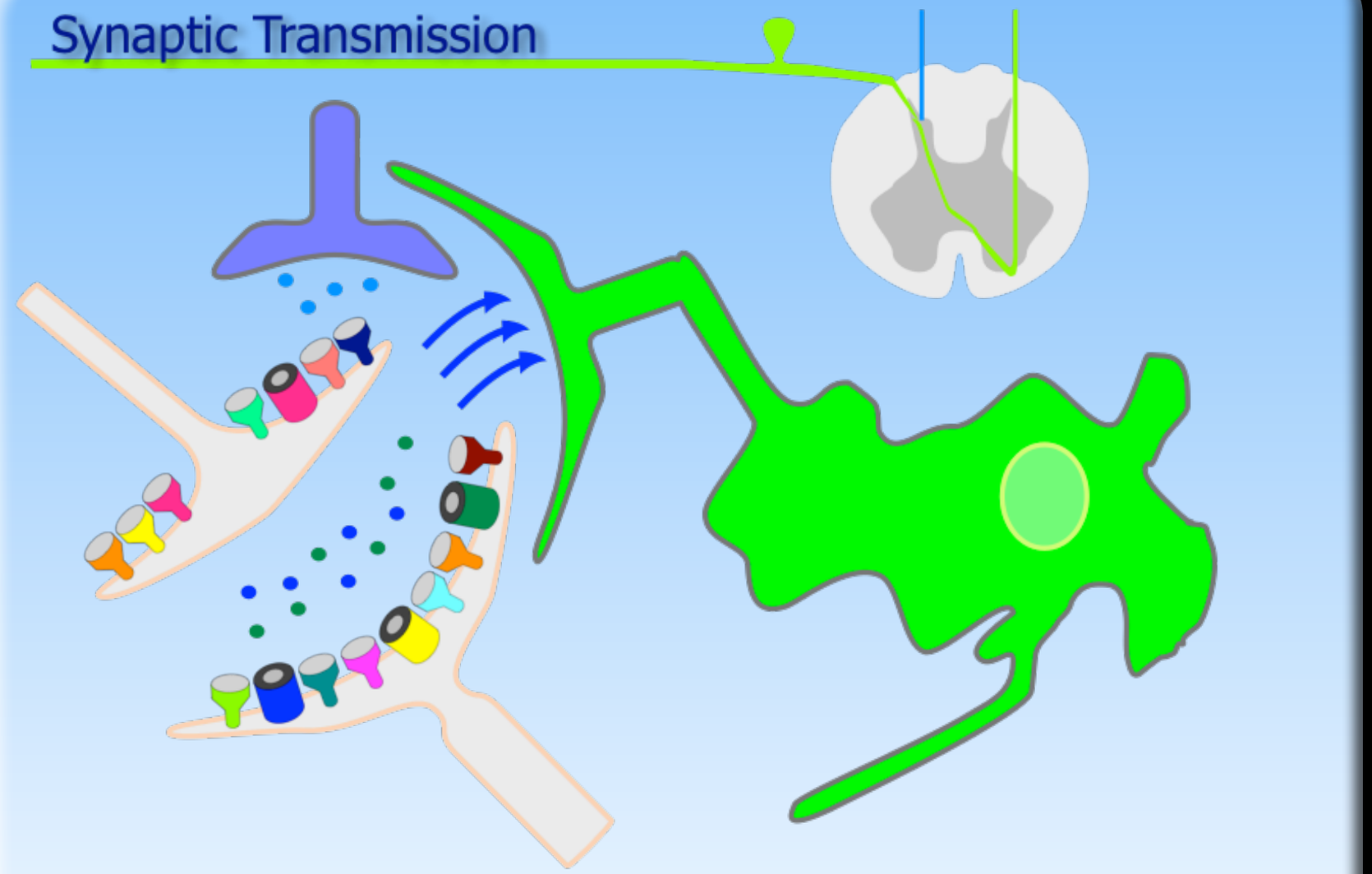
Message to brainstem

Modulated response via

- Sympathetic nervous system
- Parasympathetic nervous system

Synaptic Transmission

How does a synapse work?



Presynaptic

Electrical wave of depolarisation

Synapse

Transmitter diffuses over gap

Postsynaptic

Receptor starts new depolarisation in postsynaptic cell

Post synaptic transmission

Sympathetic nerves innervate multiple organs

- Directly release noradrenaline
- Innervate the adrenal gland and cause release of other catecholamines.

Reuptake

Removal of noradrenaline is mostly by re-uptake into the nerve cell.

- Denervation leads to reduced uptake as nerve endings die
- Exogenous agonists persist at synapses

Breakdown

Two major enzymes

- Monoamine Oxidase (MAO)
- Catechol-O-Methyl Transferase (COMT)

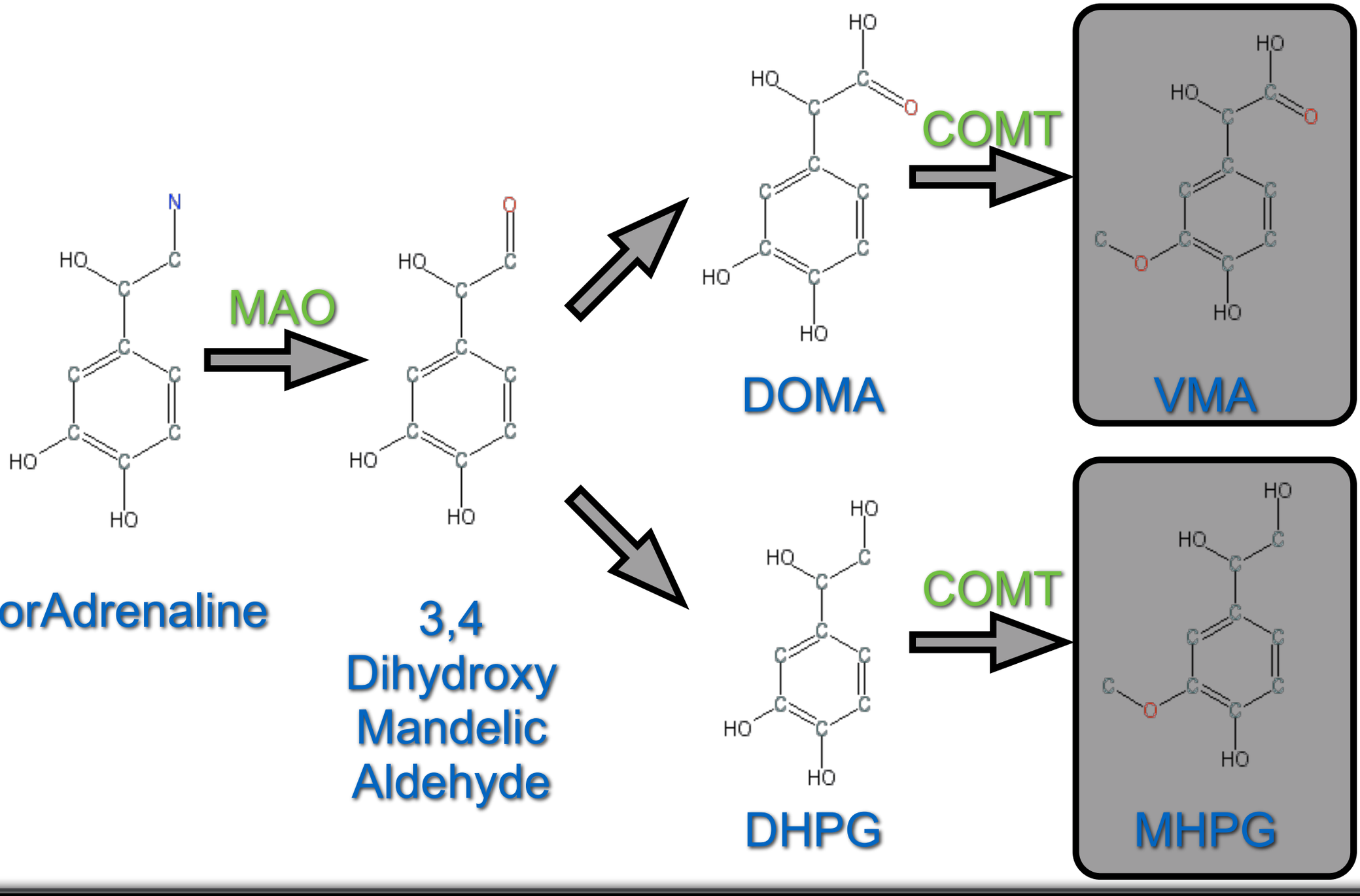
MAO

Located on the outer surface of the mitochondria

- Widely distributed

Acts to break down noradrenaline within the nerve endings.

MAO pathway


MAO
COMT
COMT
NorAdrenaline
3,4
Dihydroxy
Mandelic
Aldehyde
DOMA
VMA
DHPG
MHPG

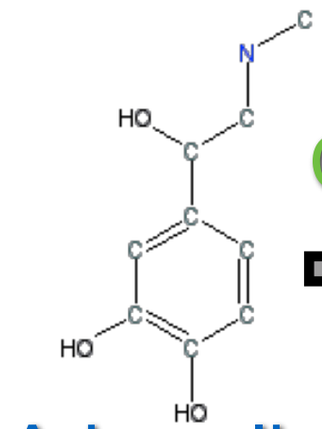
COMT

Widely distributed:

- Liver, kidney, smooth muscle
- Not found in nerve endings

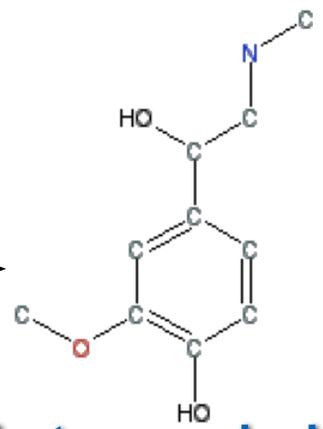
Methylation is the most common metabolic pathway for circulating catecholamines

COMT pathway



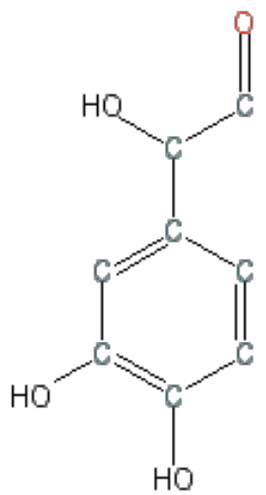
Adrenaline

COMT

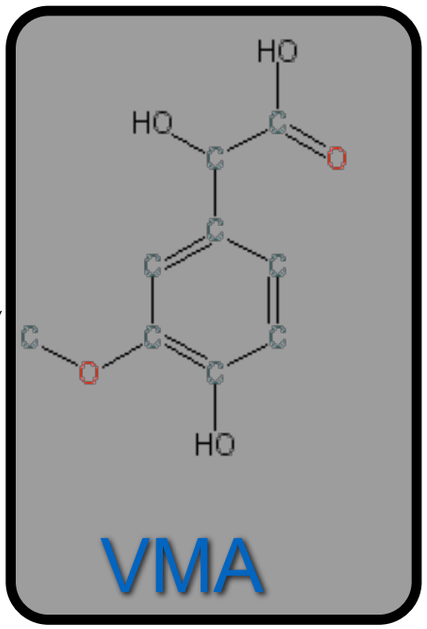


Metanephrine

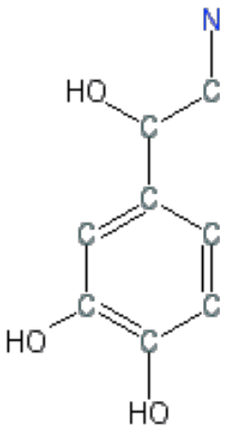
MAO



3,4 Dihydroxy Mandelic Aldehyde

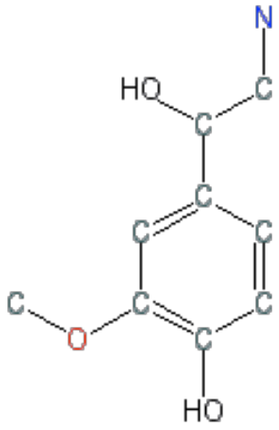


VMA



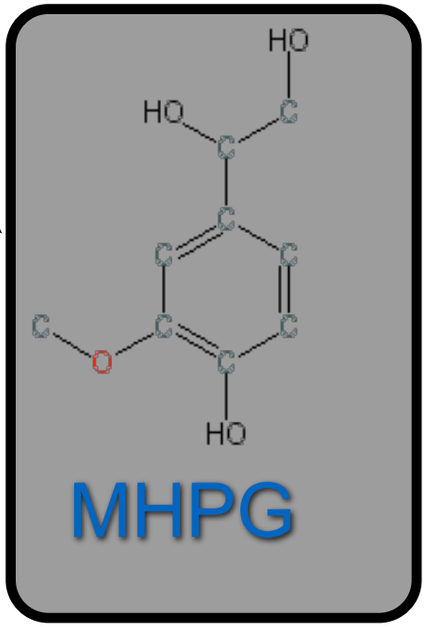
Nor Adrenaline

COMT



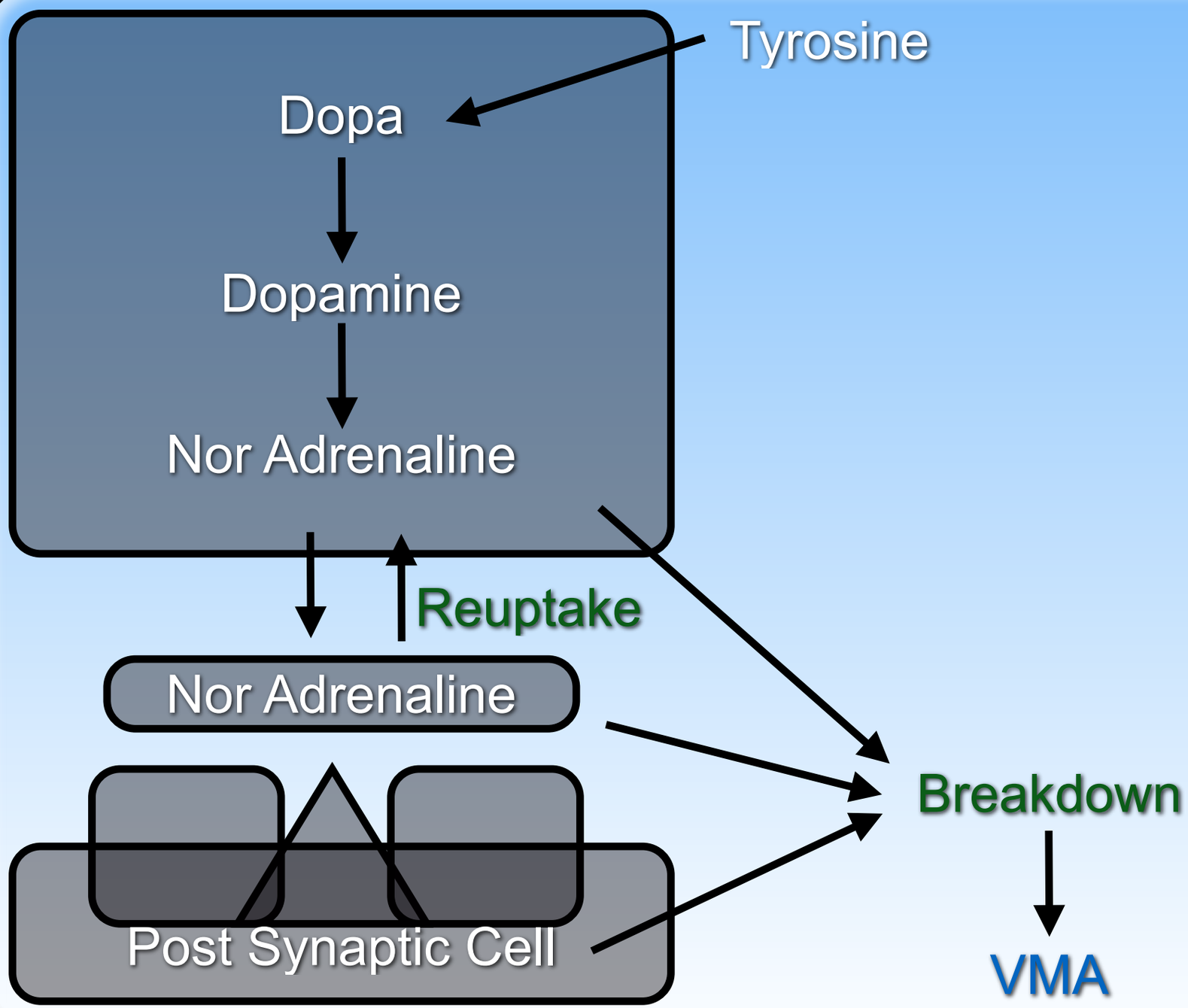
Nor Metanephrine

MAO



MHPG

Overview of biosynthesis

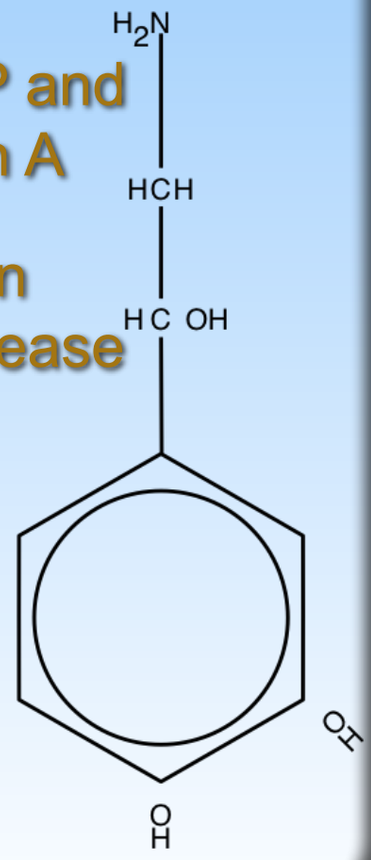


Noradrenaline

Stored in vesicles

Bound to ATP and chromogranin A

Depolarisation causes its release into synapse



End Organ Effects

Types of receptor

There are three groups of receptors

α_1: α_{1A}, α_{1B}, α_{1C}

α_2: α_{2A}, α_{2B}, α_{2C}

β: $\beta 1$, $\beta 2$, $\beta 3$

- β_1 - Heart (cardioselective)
- β_2 - Most organs
- β_3 - Fat

Organ System Effects

Cardiac & Vascular

Respiratory

Gastrointestinal & Metabolic

CNS

Cardiac

Conduction system

- SA Node
- Atria
- AV node

Atria & Ventricles

- All muscular parts of heart

β_1:
↑ Chronotrophy
↑ Inotrophy

↑ Dronotrophy
↑ Lucitrophy

Vascular

Coronary

Cerebral

Pulmonary

Splanchnic

Renal

α_1 - Vasoconstricts

β_2 - Vasodilates

β_1 - Vasodilates (Renal)

α_2 - Vasoconstricts (Coronary & Skin)

Lungs

Bronchodilation

α_1 - Gland inhibition

β_2 - Gland stimulation

β_2 - Bronchodilation

Gastrointestinal Tract

Stomach

Intestine

Gallbladder

Urinary tract

α_1 - Contraction of sphincters

α_2, β_2 - Decrease gut motility

Metabolism

Glycogenolysis

Release of FFA's

↑ Lactate release

↓ Glucose use
in some organs

α_1,β_2- Liver effects

β_2- ↑Insulin & Glucagon
α_2- ↓Insulin & Glucagon

β_1,β_3- Lipolysis

Central Nervous System

↑ Alertness

↓ Hunger

Altered HPA responses

α, β

Pharmacology
Agonists

Beta Agonists

Cardiovascular effects

Cardiac effects:

Increase HR, Contractile state. (β1)

Chronotrophy, Iontropy, Dromotropy, Lusitropy

Vascular Effects

Constricts most blood vessels (α1)

Vasodilates skeletal muscles (β2)

Clinical Use - Cardiac

Support Blood pressure & Heart Rate

Adrenaline/Epinephrine

Noradrenaline/Nor-Epinephrine

Dopamine

Synthetic agents:

Dobutamine, Isoprenaline (mostly β1)

Phenylepherine, Metaraminol (mostly α1)

Beta Agonists

Smooth Muscle

Relaxation

- Bronchii
- Gut wall
- Uterine Tone

Clinical use - β2 agonists

β2 effects predominate in lungs

Salbutamol, Salmeterol, Terbutaline

Beta Agonists

Metabolic Effects

Glycogenolysis

➡️ Raised blood glucose

Liberation of free fatty acids

Beta Agonists

If centrally acting:

- General stimulation
- Reduction in appetite
- Seizures

Centrally acting sympathetic agents

- Amphetamine and derivatives.

Alpha-1 Agonists

Alpha - 1 Agonists

Main effect is to cause vasoconstriction

- Used to raise blood pressure
- Note that blood pressure falls with many causes
  - Loss of volume (preload)
  - Loss of cardiac function (contractility)
  - Loss of vascular tone (afterload)

Alpha-2 Agonists

Alpha 2 agonists

Affect CNS and presynaptic terminals

- α2 receptor reduces α1 release

Has central effect of sedation

Alpha 2 agonists

Clonidine, Dexmetomidine

- Antihypertensive
- Sedation, Anxiolysios
- Analgesia
- Drug withdrawal

Pharmacology
Antagonists

Antagonists

Have affinity for a receptor

Do not have activity at the receptor

Block effects of the agonists

- Competitive
- Non-competitive

Alpha Blockers

Prazosin

- Blocks α1 activity
- Lowers Blood Pressure
- Treats some aspects of anxiety

Labetolol

- Blocks α and β activity

Beta Blockers

Commonly used group of drugs

- Block β activity of endogenous hormones

Many of these exist

- Atenolol, Esmolol
- Propranolol, Metroprolol
- Timolol

β blockers

Many indications for beta blockade

- Systolic heart failure
- Hypertension
- Migraine (if good penetration into brain)
- Tremor
- Tachycardias (Nodal re-entrant rhythms)

Summary

Sympathetic Nervous System

Anatomy

Physiology

Pharmacology

Structure Activity

Agonists (α & β)

Antagonists

Autonomic Pharmacology

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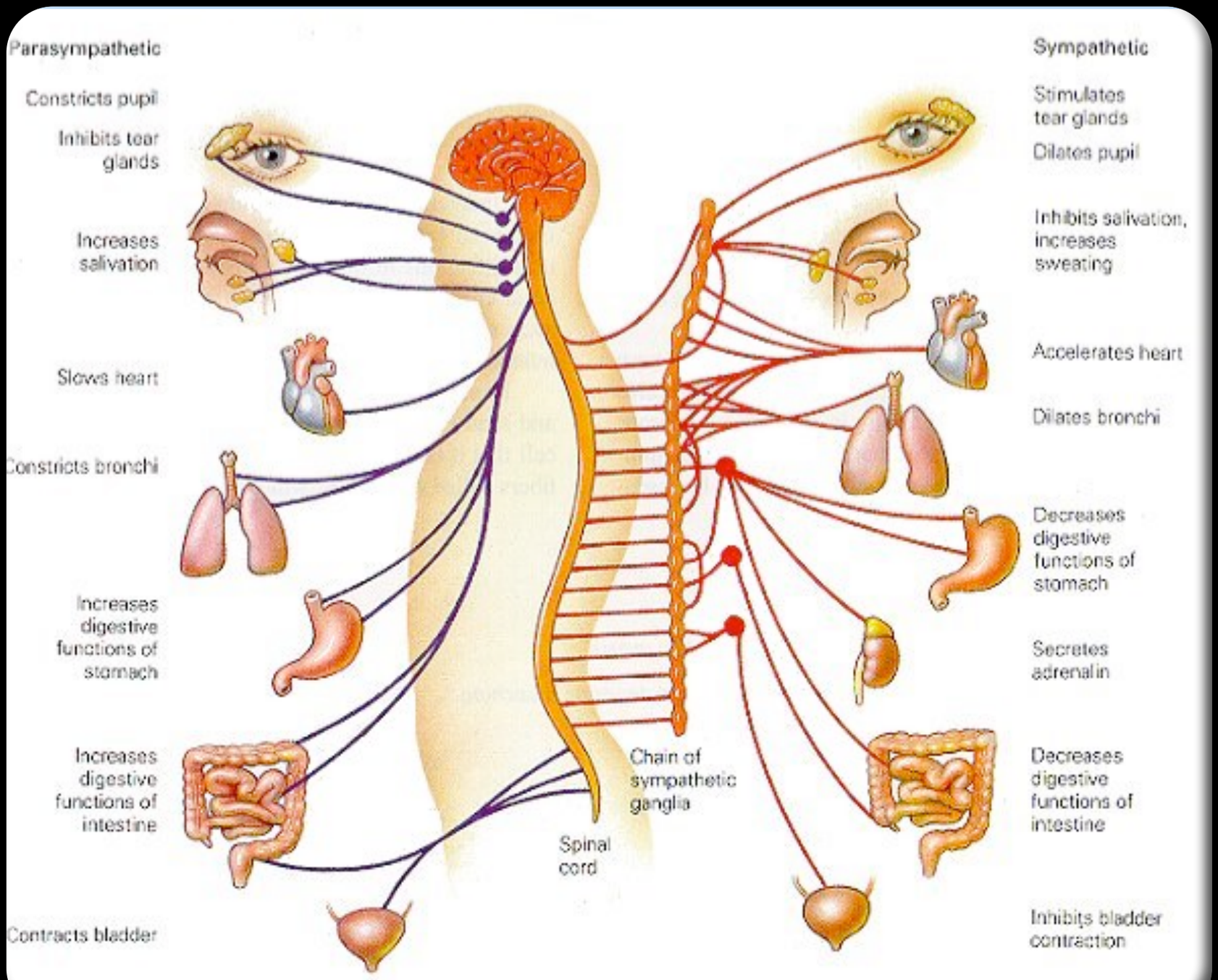
Learning Objectives

Parasympathetic Nervous System

- PNS receptors - what they are and do
- Physiological effects of the PNS
- Pharmacological agonists & antagonists

Anatomy

Parasympathetic Anatomy



Craniosacral outflow

Finely controlled

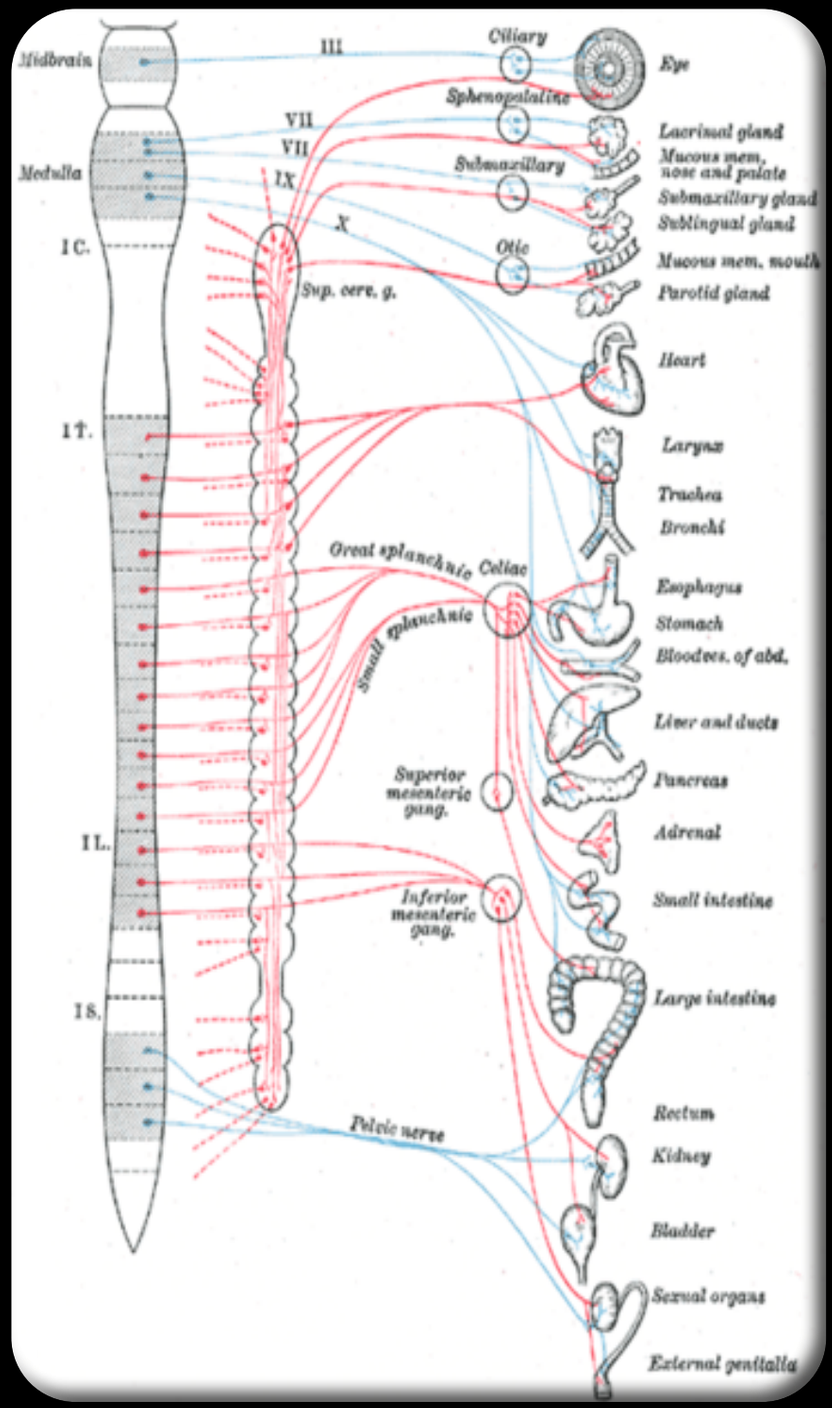
Efferent Fibres

Outflow from two areas:

- Sacral & Cranial

Ganglion inside end organ

- Long pre-ganglionic
- Short post-ganglionic
- Exception: some cranial ganglions



Parasympathetic vs. Sympathetic

Most organs have dual innervation

Generally reciprocal or opposing actions.

Occasionally:

Complimentary salivary glands, male sexual function

Single innervation of some organs

Parasympathetic: Lacrimal & GI glands

Sympathetic: Adrenal medulla, visceral arterioles, sweat glands, spleen

Physiology

Physiology

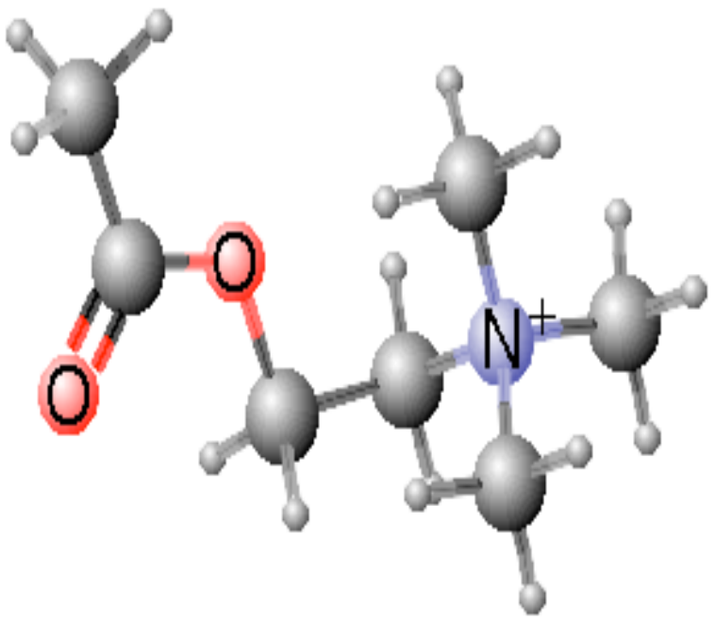
Messengers

Receptors

Secondary messengers

Effects

Acetyl Choline



Produced from

Choline

Acetyl CoA

Choline acetyl transferase

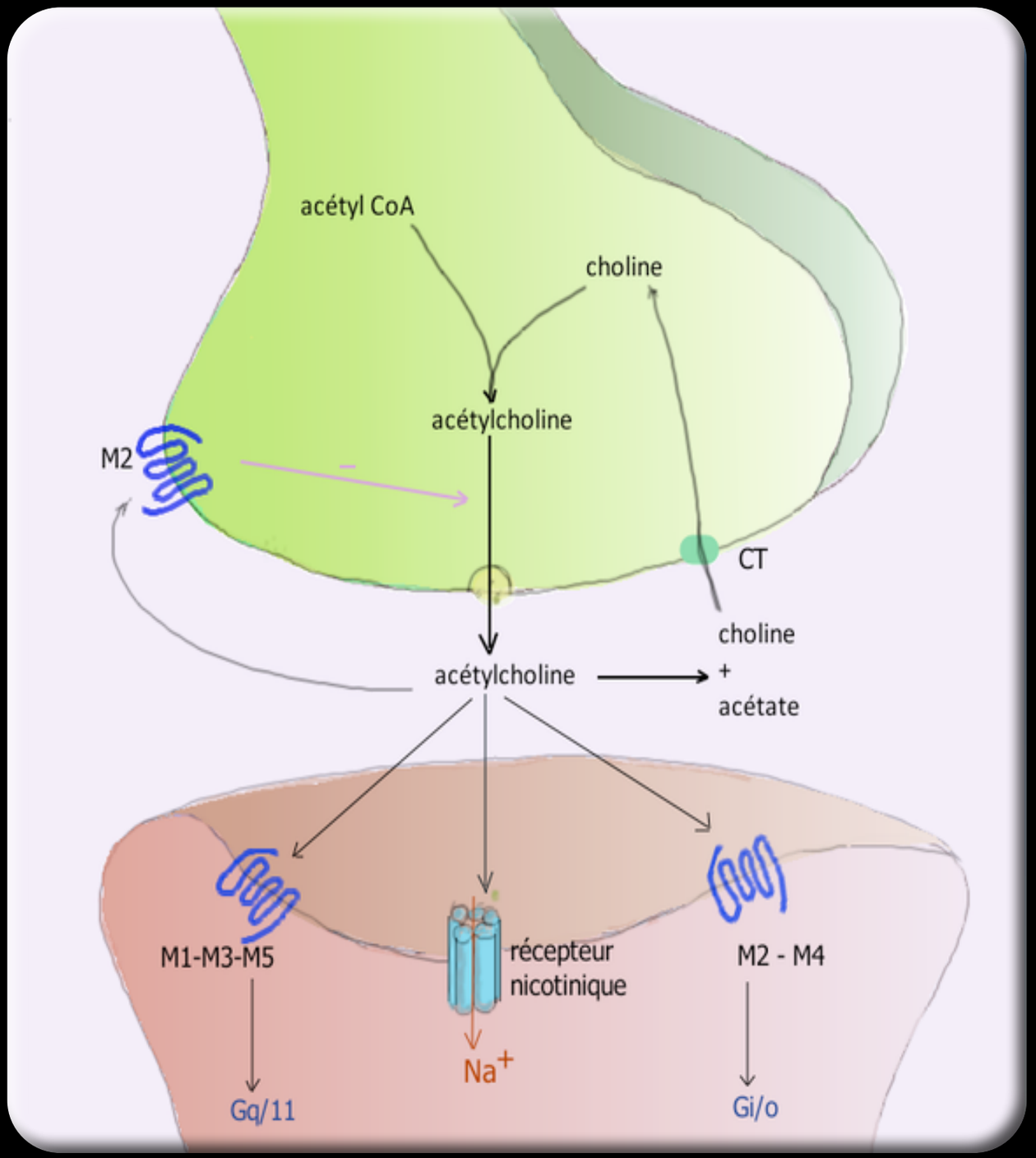
Metabolised by

Acetylcholinesterase

Choline

Acetate

Acetyl Choline Receptors



Receptors

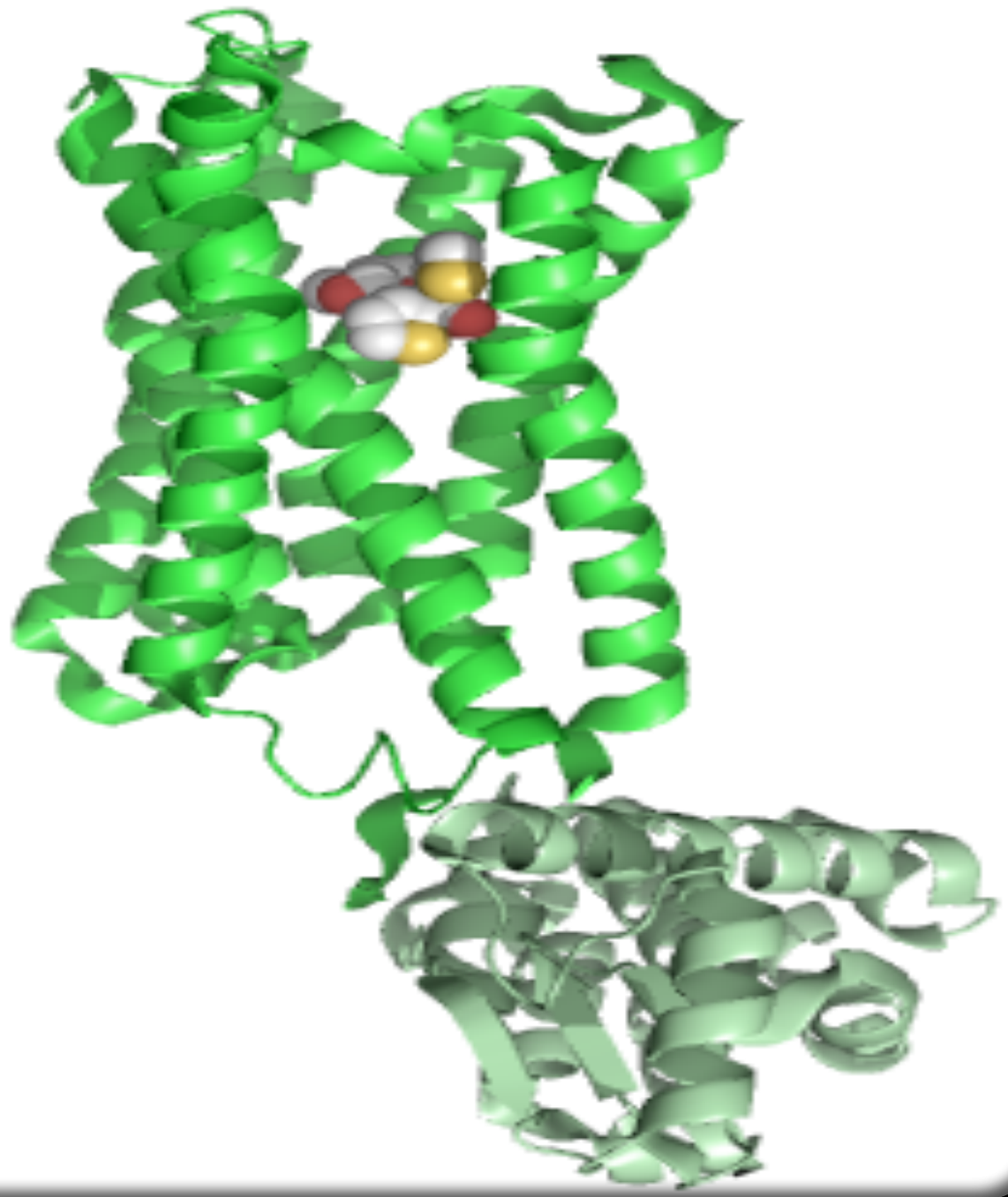
Nicotinic

Muscarinic

M1, M3, M5 (Gq)

M2, M4 (Gi)

Receptor Types



G-Protein

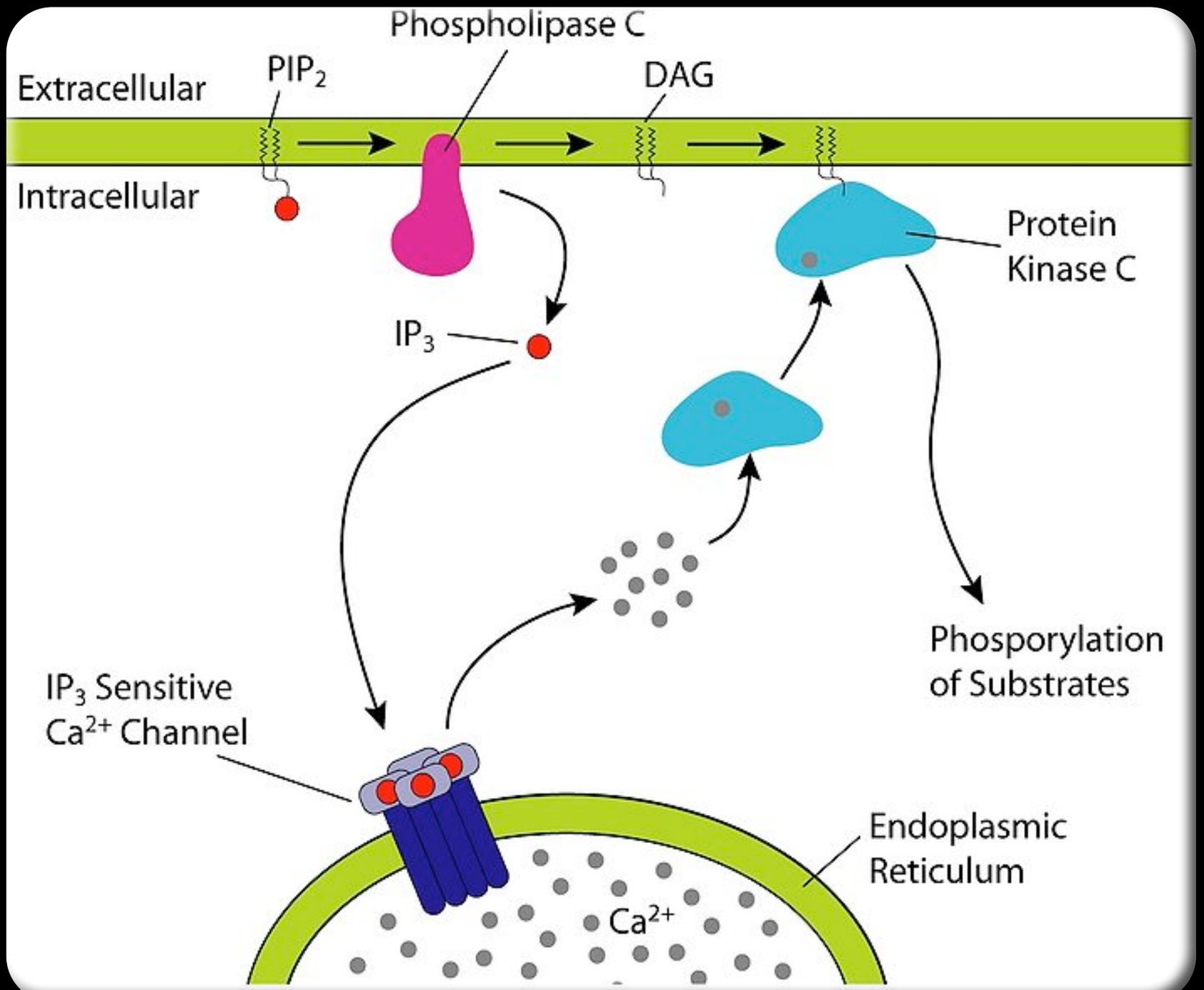
7 segments

Secondary messenger systems

Gs (Raises cAMP)

Gi (Lowers cAMP)

Secondary Messengers



IP3

Insitol Triphospate

Mediates calcium levels

Cardiovascular System

Cardiac - inhibiting effects

Chronotrophy, inotrophy, dronotrophy & lucitrophy

Vascular - Dilation effects

Pulmonary, Cardiac & most other places

Mediated by M3 receptor / Release of EDRF (NO)

Respiratory Effects

Respiratory system

↑ Tracheobronchial secretion

Bronchoconstriction

GIT Effects

Gut motility increases

- Tone, amplitude of contractions & peristalsis

Secretions increased

- Salivation & Gastric secretions (Acid)

Sphincter relaxation

Glycogen synthesis in liver

Glandular effects

Adrenal medulla

Increased Adrenaline & Noradrenaline

Increased glandular secretion

Sweat / Tears / Bronchial tree / Digestive

Exocrine glands

Other Effects

Urogential

Ureter motility increased / Detrusor contraction

Decreased bladder capacity & Increased voiding pressures

Occular

Miosis / Lacrimation / Reduced intraoccqular pressures

Summary

- Messengers
- Receptors
- Secondary messengers
- Effects

Pharmacology

Cholinesterase inhibitors
Agonists

Basis of pharmacology

Directly activating all of parasympathetic system doesn't work well.

Blockade of breakdown of acetylcholine is more specific and effective

Cholinesterases

Acetylcholinesterase

Nerve endings / red blood cells

Butyrylcholinesterase (“pseudo”)

Made in liver, found in plasma

Important for metabolism of some drugs:

Succinylcholine, mivacurim, esmolol, procaine, heroin, cocaine

Acetylcholinesterase inhibitors

Inactivation of acetylcholinesterase:

Higher levels of AcH

Longer duration of action

AcH inhibitors bind to enzyme site and block its ability to break down AcH

Lipid Solubility

Water-soluble inhibitors

Hydrolyzed within 2-8 hours

Most therapeutic agents are water soluble

Lipid-soluble inhibitors

Form stable complex with cholinesterase

Released over periods of days to weeks.

Classification

Carbamates (reversible & water soluable)

- Physostigmine
- Neostigmine
- Pyridostigmine, Edrophonium

Centrally Acting Agents

- Donepezil

Classification

Organophosphates (irreversible & lipid soluable)

- Isoflurophate (Pralidoxime antidote)
- Echothiophate

Insecticides: Malathion, Parathion

Nerve Gases: Sarin, Tabun

Clinical use of anticholinesterases

Reversal of neuromuscular blockade

Myasthenia Gravis

Side Effects

All these agents cause significant rises in acetylcholine levels.

Muscarinic Effects

"Amplify" endogenous acetylcholine.

Eye (Miosis)

Resp (Bronchoconstriction)

CVS (Hypotension, bradycardia)

Urological (Urination)

Muscarinic Effects

GI effects

- Diarrhoea
- Vomiting & Salivation

CNS effects

- Tremor & Anxiety
- Convulsions & Coma

Nicotinic Effects

AcetylCholine is a messenger for the neuromuscular junction.

- Nicotinic receptor at this location
- Different from muscarinic (autonomic) effects

Skeletal muscle

- Fasiculations

Side Effects

Can be predicted from the physiology of acetyl choline

- Muscarinic
- Nicotinic

DUMBELS

Diarrhea, Urination, Miosis, Bronchoconstriction, Excitation (of skeletal muscle & CNS), Lacrimation, and Salivation and Sweating

Toxicity

Toxicity is seen with:

- Clinical overdosage
- Pesticide poisoning
- Chemical warfare (Sarin, Soman)

Management of toxicity

Block excess AcH

- Atropine +/- nicotinic blocker (eg vecuronium)

Pralidoxime (2-PAM)

- N+ interacts with the anionic site
- Donates the proton from the NOH group to the phosphorylated enzyme
- Dephosphorylation of the enzyme

Cholinesterase inhibitors Summary

Mechanism of action

Classification

Indications

Contraindications

Side Effects

Toxicity

Anticholinergic agents

Chemistry

Widely found in nature

Atropine

Deadly nightshade (Atropa Belladonna)

Datura Stramonium (Jamestown Weed)

Scopolamine

Hyoscyamus niger, henbane

Atropine

- Ester of tropine and tropic acid
  - Nonselective competitive antagonist
  - M1 & M2 receptors
- Minimal effect at nicotinic receptors

Atropine: Indications

Cardiovascular

Respiratory / Secretory

Acid suppression (Obsolete)

Sedation

In reversal of blockade

Atropine: Dosage

5-10 mcg/kg (0.3-0.6 mg)

Larger doses used

- In reversal of blockade
- In myasthenic syndromes
- With organophosphate toxicity
- In severe bradycardias

Glycopyrrolate

Originally used in the treatment of peptic ulcer disease

Anaesthetic premedicant

Antisialogogue action

- long duration
- potency relative to atropine ~ 2:1

Ipratropium

Anticholinergic that is poorly absorbed

Useful topically

- Asthma

Toxicity

- Cardiovascular
- CNS
- GIT
- Urogenital