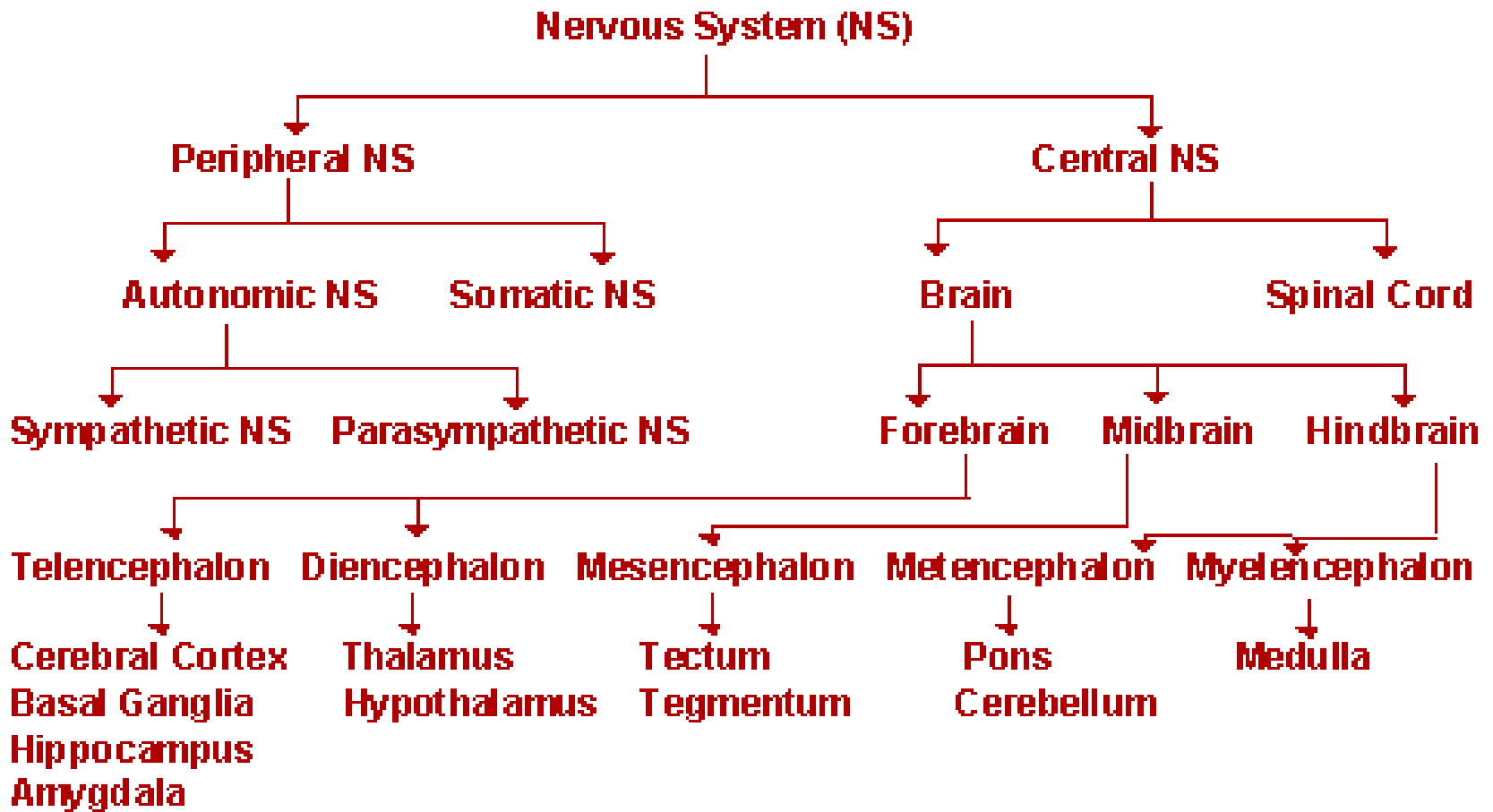


NEURO HUMORAL TRANSMISSION



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Autonomic Nervous System

- ▶ ANS is a peripheral complex of nerves, plexus, & ganglia that are organized to modulate the involuntary activity of secretory glands, smooth muscles & visceral organs.
- ▶ The ANS also has been termed = The Visceral / Involuntary / Vegetative Nervous system.
- ▶ In periphery = ANS = Nerves, Ganglia, Plexus = innervation to the heart, blood vessels, secretory glands, visceral organs, smooth muscles in various tissues

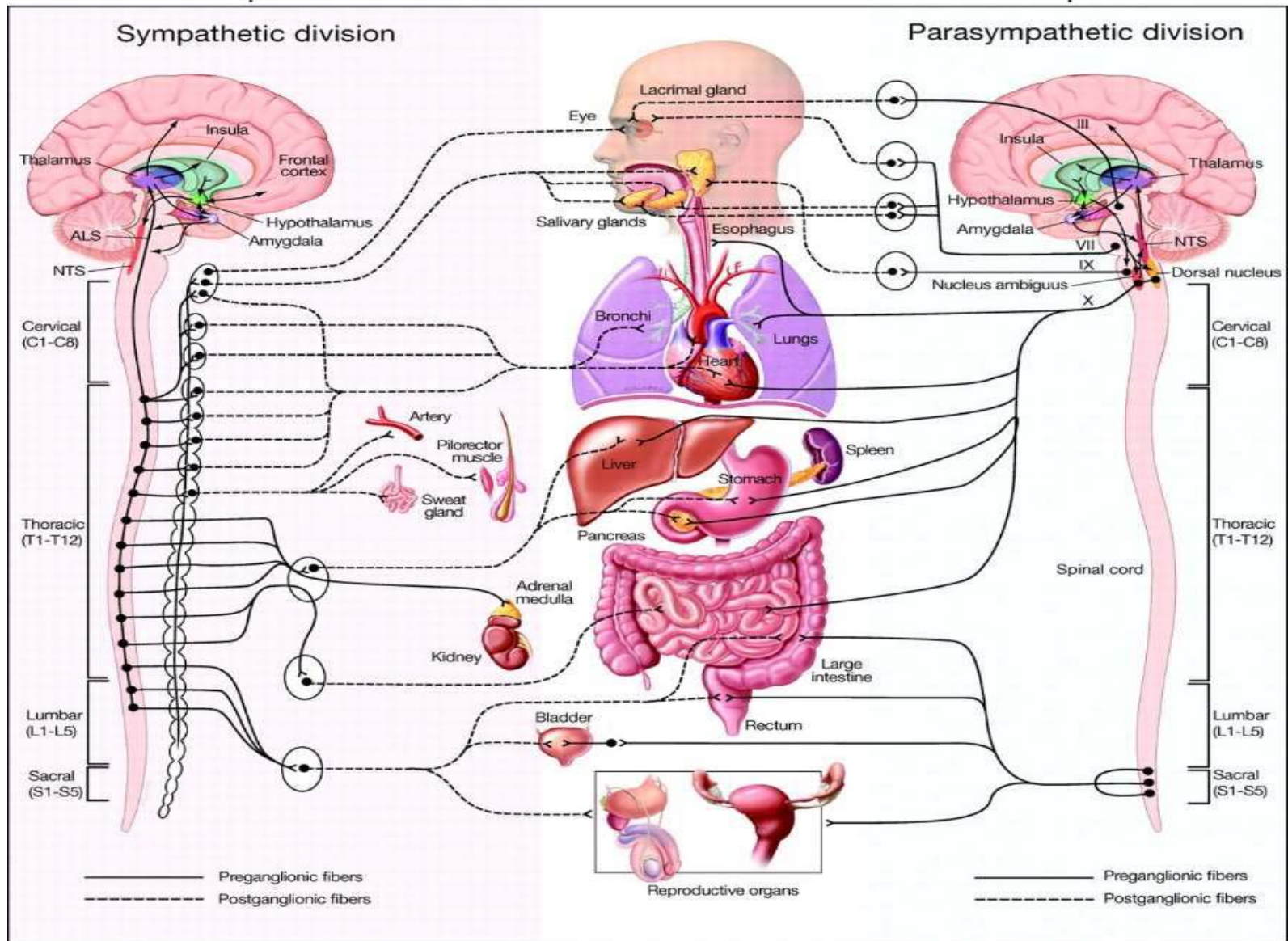


Efferent nerve tracts/outflows

- ▶ Supply motor innervations to visceral structures
- ▶ The efferent segment of the ANS divided into 2 segments
 - ▶ The Sympathetic Nervous System
 - ▶ The Parasympathetic Nervous System



Autonomic Nervous System



Comparison b/w sympathetic & parasympathetic NS

SYMPATHETIC NERVOUS SYSTEM

- Thoraco-lumbar outflow : T 1-12, L 1-3.
- Preganglionic fibre short, myelinated.
- Postganglionic fibre long, nonmyelinated.
- Ganglia types-paravertebral
 - -prevertebral
 - -terminal
- Intense ramification(1:20)= Very diffuse
- Discharge=generalized action
- Catabolic in nature (expenditure of energy).

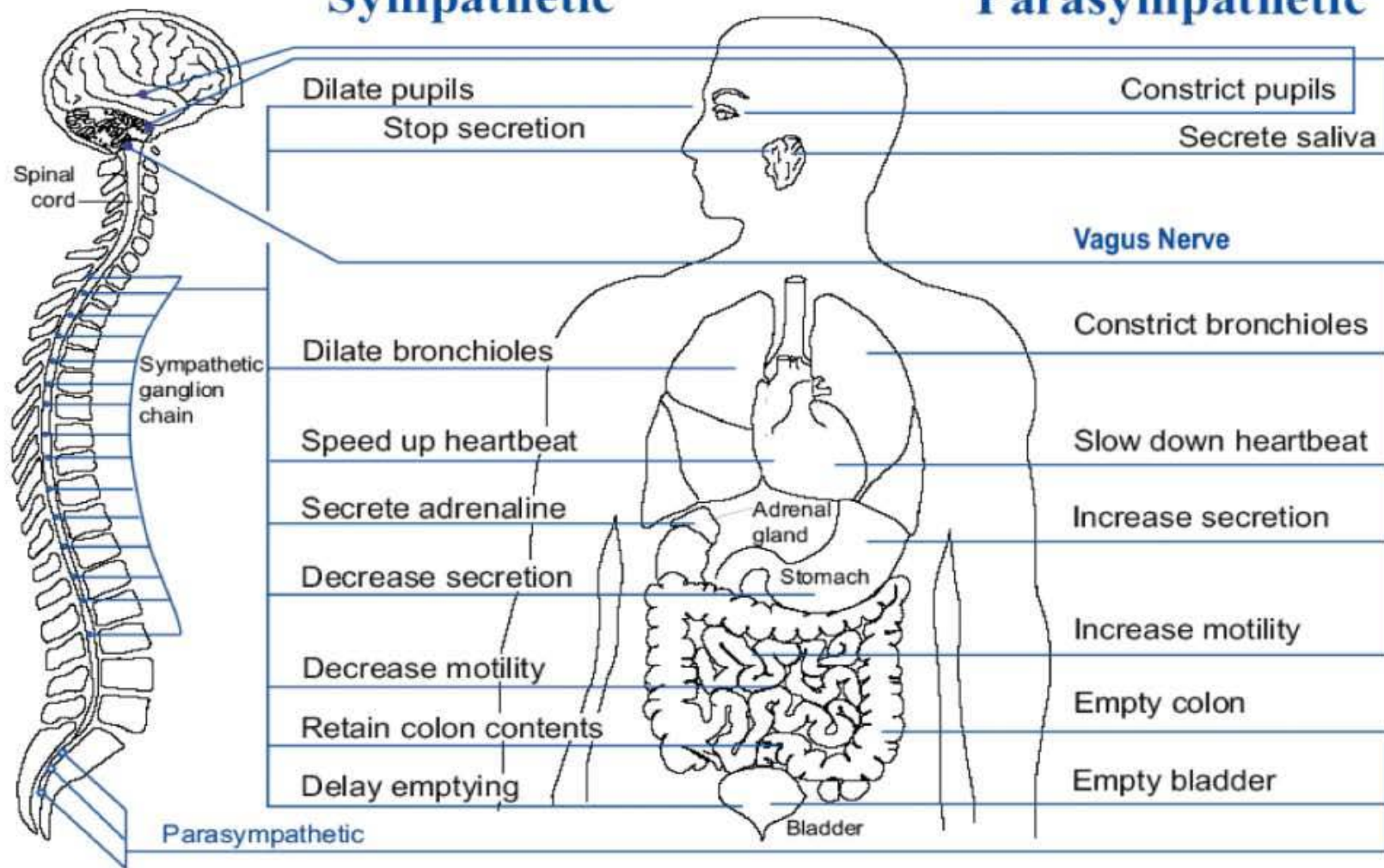
PARASYMPATHETIC NERVOUS SYSTEM

- Cranio-Sacral outflow : Cr 3,7,9,10 ; S 2-4.
- Preganglionic fibre long, myelinated.
- Postganglionic fibre short, non myelinated.
- Ganglia types-ciliary
 - -submaxillary & parotid
 - -terminal
- Limited ramification(1:1)= Discrete discharge=affects specific effector system, individually.
- Anabolic in nature (conservation & restoration of energy)



Sympathetic

Parasympathetic

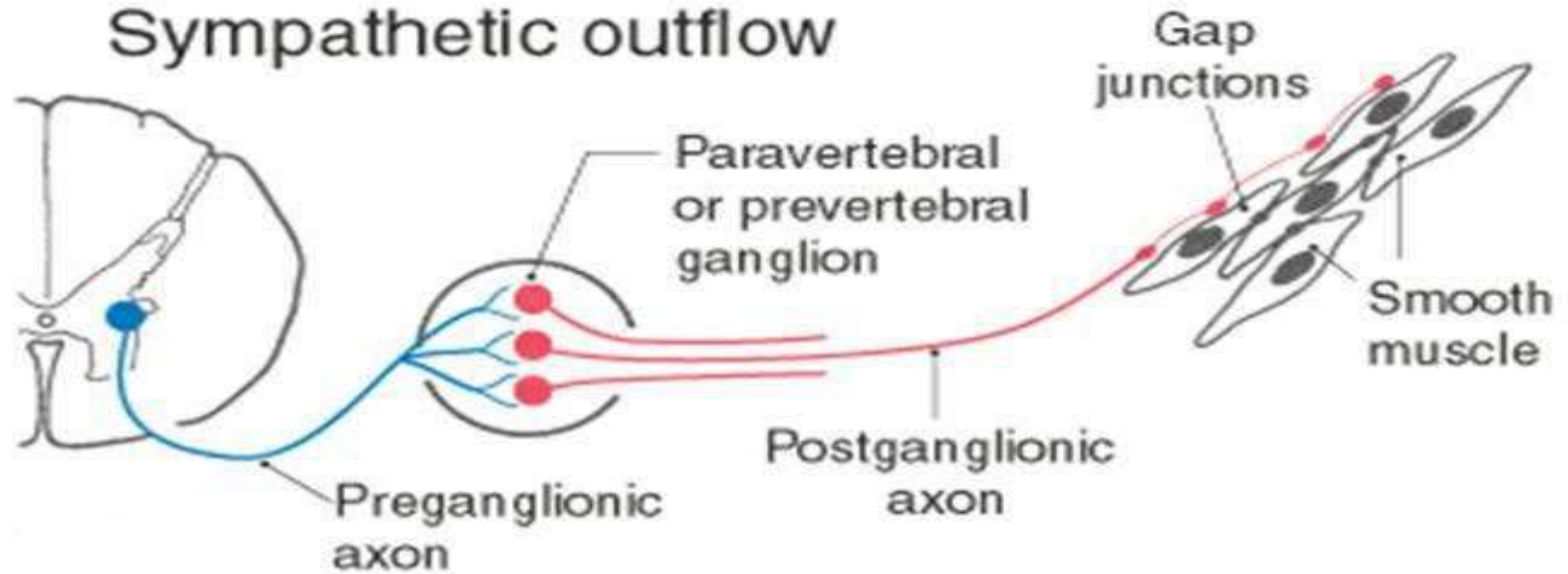


The Synapse / Junction.

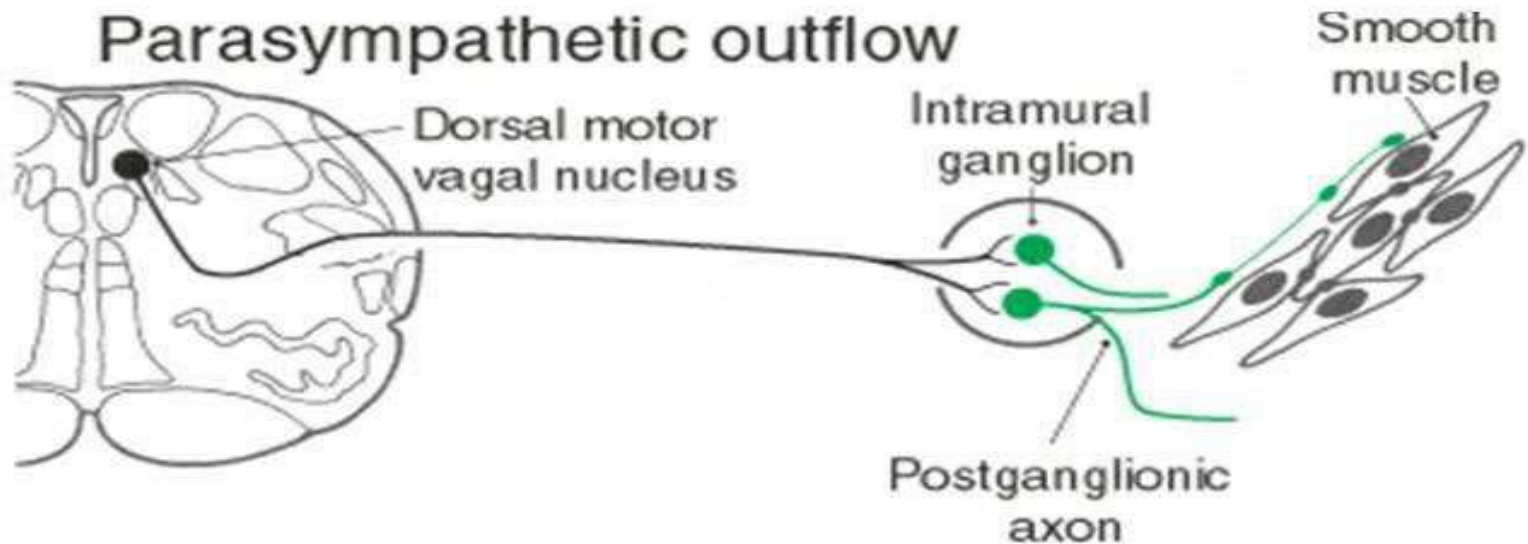
- ▶ Synapse of a preganglionic axon with a ganglionic neuronal body occurs outside the CNS within an autonomic ganglion.
- ▶ An axon of a ganglionic cell passes peripherally & innervates its effector organ / organ substructures.
- ▶ The junction of a post ganglionic axonal terminal with its effector cell is termed as Neuro-effector junction.

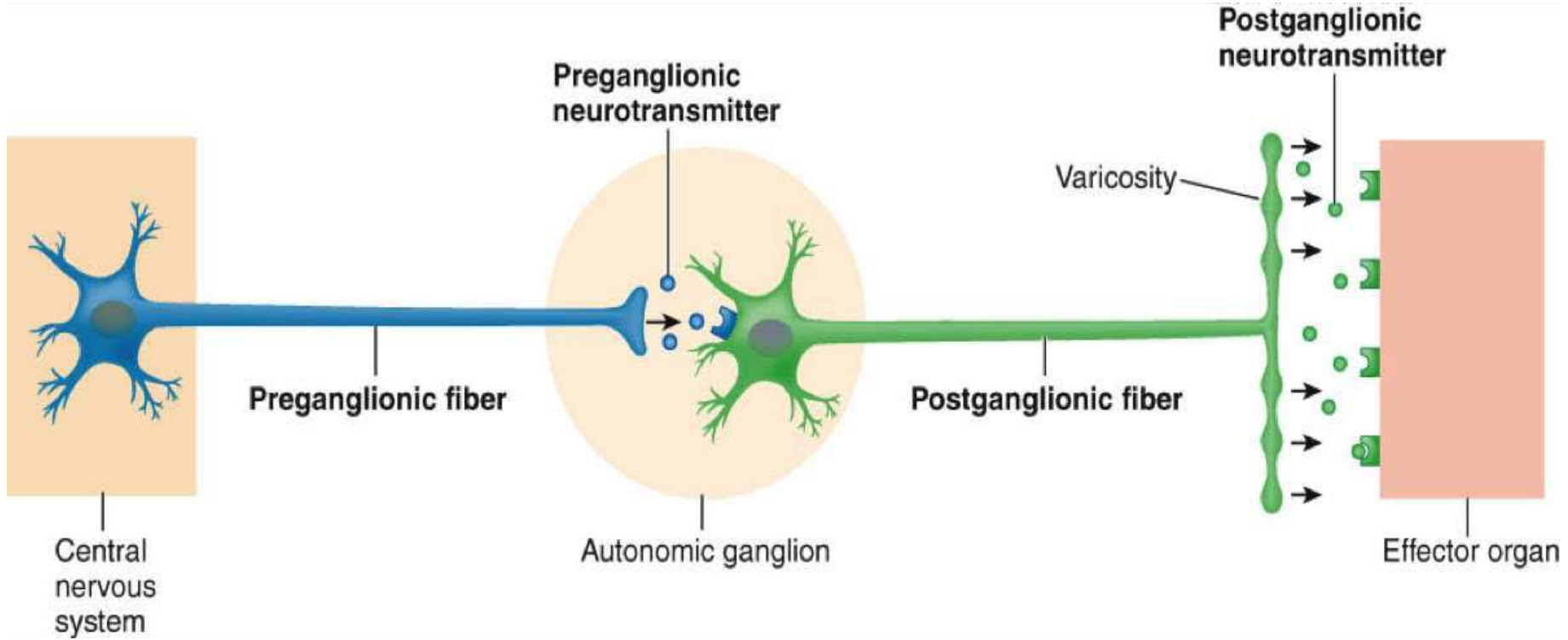


Sympathetic outflow



Parasympathetic outflow





NEUROTRANSMISSION

- ▶ Information is communicated from nerve to nerve & from nerve to effector organ by a process termed neurohumoral transmission.
- ▶ *Neuro-humoral transmission involves release from a nerve terminal of a chemical neurotransmitter that reacts with specialized receptors area on the innervated cell. Activation of the receptor instigates*
- ▶ *characteristic physiologic responses in the effector cells*



Neurohumoral transmission

The transfer of nerve impulse from presynaptic to post synaptic neuron by means of a humoral agent e.g. biogenic amine, an amino acid or a peptide.

❖ Acetylcholine (Ach) and Norepinephrine are major neurotransmitters of nervous system.

❖ CRITERIA FOR NEUROCHEMICAL TRANSMITTER:

1. It must be present in the nerve endings.
2. The neuron must contain the enzymes necessary for its manufacture and release.
3. The presence of various precursors in the synthetic pathway should be demonstrable.



4. There should be system for the inactivation of the transmitter.
5. During nerve stimulation, the substance should be detectable in extracellular fluid collected from the regions of the activated synapses.
6. When applied to the post-synaptic cell body, the substance should mimic the action of the synaptically released transmitter.
7. Drugs which are thought to produce their effects by interaction within the transmitter should be shown to interact with it, in the predicted manner, under experimental conditions.



PRINCIPLES OF CHEMICAL TRANSMISSION

- These include
 - a) DALE's principle.
 - b) Denervation supersensitivity.
 - c) Neuromodulation.
 - (i).pre-synaptic modulation.
 - (ii).post –synaptic modulation.



(A).DALE'S PRINCIPLE

- “A mature neuron releases the same neurotransmitter at all of its synapses”.
- Later on it was found that neurons release more than one neurotransmitters as in cotransmission.
- e.g. at noradrenergic synapses along with Norepinephrine some dopamine, NPY, and PGs are also released.



(B).DENERVATION SUPERSENSITIVITY

- *“When a nerve supplying the skeletal muscle, smooth muscle or an exocrine gland is sectioned and undergo degeneration ,the muscle or gland slowly becomes hyper responsive to the neurotransmitter which was secreted from the nerve ending.”*
- **e.g.** the skeletal muscle which normally responds to injected Ach only if large dose is given into arterial blood supply, will after denervation respond by contracture to much smaller amounts.
- Other organs like salivary glands and blood vessels show similar supersensitivity to Ach and NA when post ganglionic nerves degenerate.



MECHANISM OF DENERVATION SUPERSENSITIVITY

It includes;

1. Proliferation of receptors.
2. Loss of mechanism of transmitter removal.
3. Increased post junctional responsiveness.

1. PROLIFERATION OF RECEPTORS:

- Particularly in skeletal muscles.
- Normally Ach receptors are present on end plates but after denervation there is 20-fold increase in receptor number and the receptors are spread over the whole surface.
- But there are cases where no such change occur.



2. Loss of mechanism of transmitter removal:

- At noradrenergic synapses, loss of neuronal reuptake of Noradrenaline and at cholinergic synapses loss of cholinesterase contribute to supersensitivity.

3. Increased post junctional responsiveness:

in some cases postsynaptic cells become super sensitive without a corresponding increase in the number of receptors. Thus smooth muscle cells partly depolarized and hyper excitable.



(C).NEUROMODULATION

i. PRESYNAPTIC MODULATION:

- *Presynaptic terminals that synthesize and release transmitters are often sensitive to transmitter substances and to other substances.*
- Such presynaptic effects commonly inhibit transmitter release but may enhance it also.
- It involves two types of presynaptic interactions;
 - (1).heterotropic interactions.
 - (2).homotropic interactions.



1. HETEROTROPIC INTERACTIONS

- *“One neurotransmitter affects the release of another neurotransmitter”.*

Examples:

Noradrenergic and cholinergic nerve terminals often lie close together in ‘myenteric plexus’ and Noradrenaline inhibit the release of Ach.

In heart Ach inhibit NA and NA inhibit Ach release. This is ‘mutual presynaptic inhibition’.



2. HOMOTROPIC INTERACTIONS

- “Transmitter by binding to autoreceptors ,affects the nerve terminals from which it is being released.”
- This type of autoinhibitory feedback acts powerfully at noradrenergic nerve terminals.

Examples:

Released NA can inhibit by at least **90%** of further release of NA.

Similarly Ach release is modulated by autoinhibitory feedback that involves presynaptic muscarinic AchR.

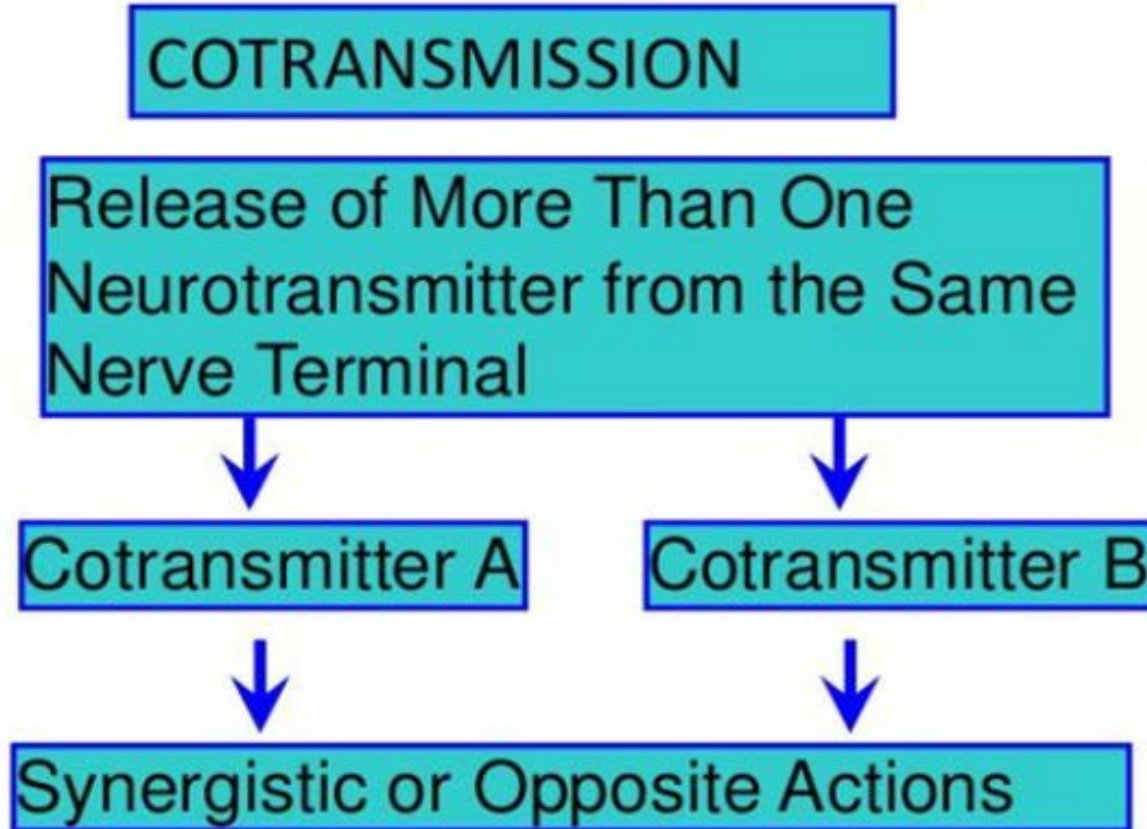


ii. POSTSYNAPTIC MODULATION

- *Chemical mediators act on the postsynaptic structures to alter their excitability or spontaneous firing pattern due to changes in Calcium /or potassium channel function, mediated by second messengers.*
- **Examples:**
- Ach and peptides e.g. substance P produced excitatory effects on many peripheral and CNS neurons mainly from a decrease in K^+ permeability. Conversely, the inhibitory effect of various opiates is mainly due to increased K^+ permeability.



COTRANSMISSION



Hypothesis about Neurotransmission

- ▶ Neurotransmitters in the periphery & central N S, once was believed to confirm the hypothesis that each neuron contains only one transmitter substance.

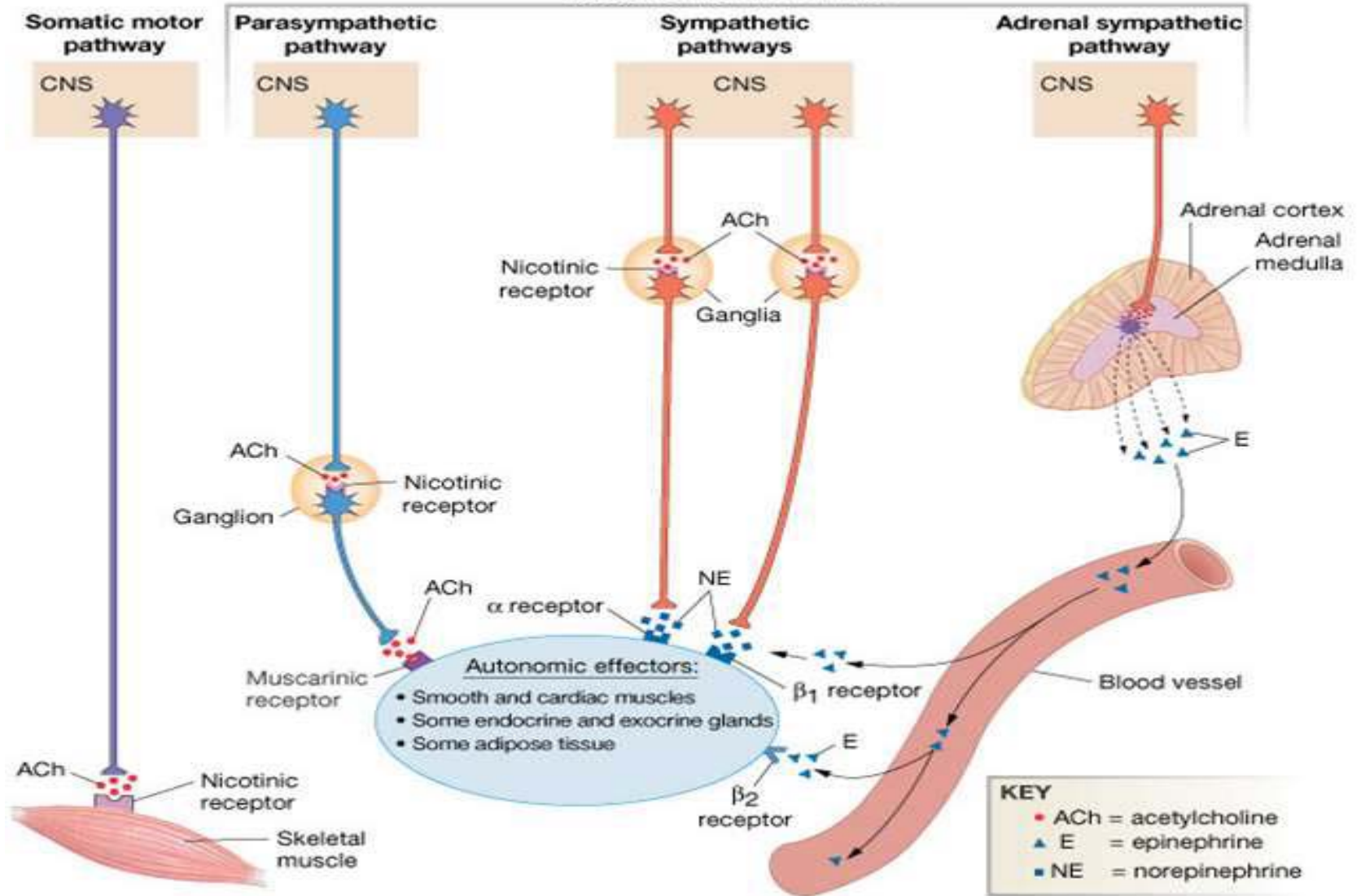
However,

- ▶ I. Peptides – enkephalin, substance P, VIP, neuropeptide Y, somatostatin.
- ▶ II. Purines – ATP / Adenosine.
- ▶ III. Small molecules – Nitric-Oxide.

Have been found in nerve endings. These substance can depolarize or hyperpolarize nerve terminals & postsynaptic cells.



AUTONOMIC PATHWAYS



Classical biogenic amine neurotransmitter

- ▶ Enkephalins ~ post ganglionic sympathetic neurons
~ adrenal medullary chromaffin cells
- ▶ VIP ~ peripheral cholinergic neurons that innervates exocrine glands (gut, Pancreas)
- ▶ Neuropeptide Y ~ sympathetic nerve endings (Brain, Spinal cord)



Neurotransmitters & their location

Neuro transmitters	Location
Acetylcholine	<ul style="list-style-type: none">- Parasympathetic ganglia- Sympathetic ganglia- Parasympathetic neuro effector junction
Norepinephrine	<ul style="list-style-type: none">- Sympathetic neuro effector junction
exceptions	<p>Ach @ sympathetic neuro effector junction of sweat gland.</p> <p>Neurotransmitter @ parasympathetic junction of erectile tissues of genitalia is not Ach(Klinge & Sjostrand 1974; Klinge et al 1978)</p>



Physiological events involved in NT

- ▶ Axonal conduction
- ▶ Neuro-transmitter release (Junctional transmission)
- ▶ Receptor event
- ▶ Initiation of post Junctional activity
- ▶ Destruction/Dissipation of the transmitter
- ▶ Non electrogenic functions



- **NEUROHUMORAL TRANSMISSION**

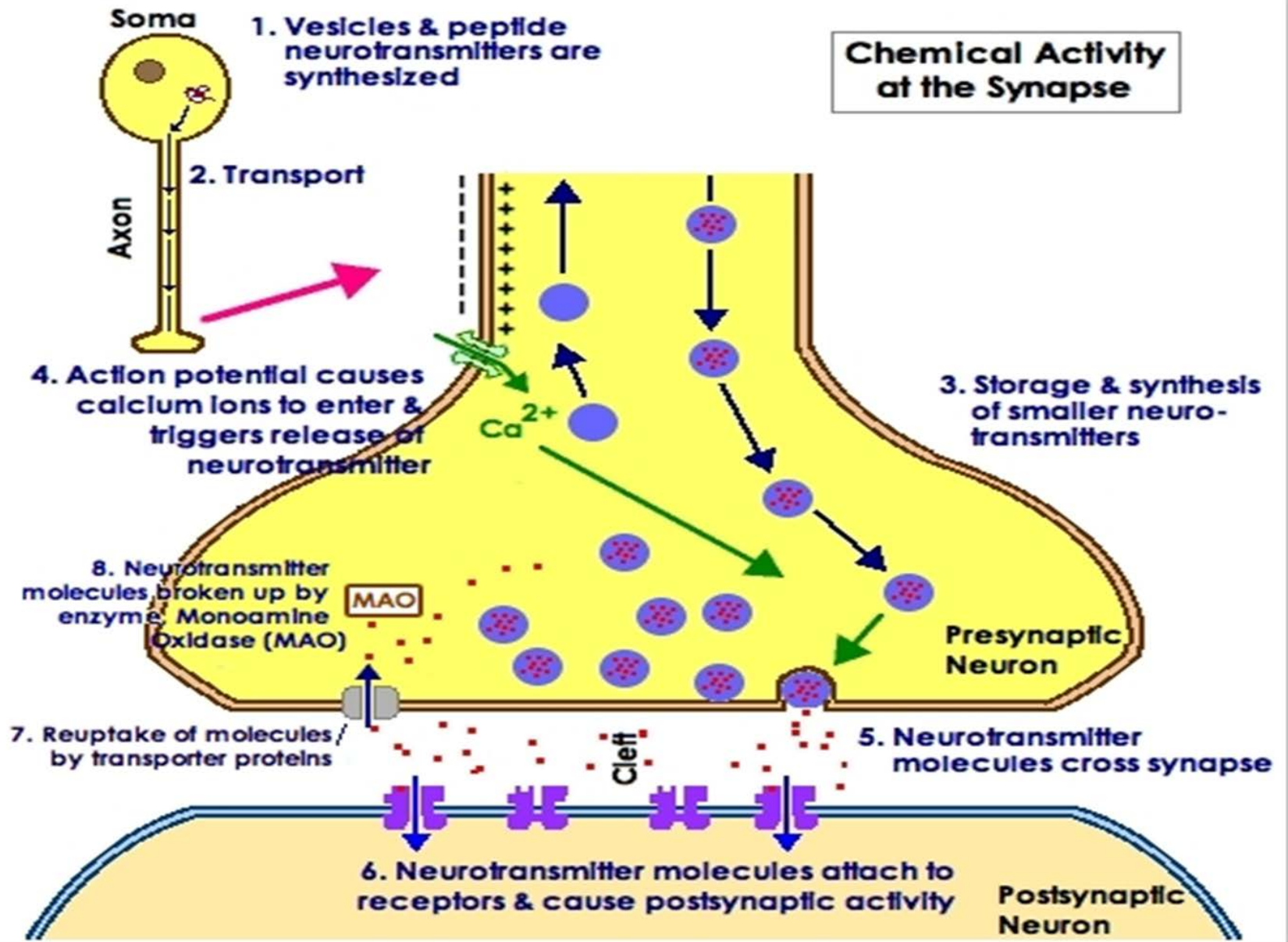
- Neurohumoral transmission implies that nerves transmit their message across synapses and neuroeffector junctions by the release of humoral (chemical) messengers

- **STEPS IN NEUROHUMORAL TRANSMISSION:**

- 1) Impulse conduction
- 2) Transmitter release
- 3) Transmitter action on post synaptic membrane
- 4) Post junctional activity
- 5) Termination of transmitters



Chemical Activity at the Synapse



1. Axonal conduction

- ▶ Refers to passage of an impulse along nerve fibre.
- ▶ A supra threshold stimulus initiates a localized change in the permeability of the axonal membrane.
- ▶ Action potential
 - Depolarization \longrightarrow influx of Na^+
 - Repolarization \longrightarrow efflux of K^+
 - inward movement of Ca^{++} @ nerve terminal
- ▶ Action potential is self propogating & is conducted along an axonal fibre

Axonal conductance & its Response to various drug

- ▶ Insensitive to most of the drugs.
- ▶ Local anesthetics must be used in high concentration in immediate contact with the nerve before excitability is blocked.
- ▶ 1. Tetrodotoxin & Saxitoxin – selectively blocks axonal conductance
- ▶ 2. Bactrachotoxin –selective increase in permeability of the Na⁺ channel, which induces persistent depolarization
- ▶ 3. scorpion toxins –causes persistent depolarization by inhibiting the inactivation process



2. Neurotransmitter release

- ▶ The arrival of AP @ the terminal initiates a series of events that triggers transmission of an excitatory & inhibitory impulse across the neuro effector junction or synapse.
- ▶ The AP causes the synchronous release of several hundred quanta of neurotransmitter
- ▶ Depolarisation of the axonal terminal triggers this process.
- ▶ Types of NT: the non peptide NT the peptide NT



3. Receptors of neurons

- ▶ Soma dendritic receptors – when activated, primarily modify functions of soma dendritic region viz protein synthesis & AP generation.
- ▶ Presynaptic receptors –when activated, they modify functions of the terminal region viz synthesis & release of NT.
- ▶ Hetero receptors –presynaptic receptors response to NT release, neuromodulators or neurohormones released from adjacent neurons.

Eg: NE influence Ach parasympathetic neurons by acting on α_2A , α_2B , α_2C receptors.

- ▶ Acetylcholine influence the release of NE from sympathetic neurons by acting on M_2 & M_4 receptors.



Combination of the transmitter with post junctional receptors & production of the post junctional potential.

- ▶ A generalized increase in the permeability to cation Na^+ = localized depolarization of the membrane = Excitatory Post Synaptic potential.
- ▶ A selective increase in permeability to anions Cl^- = actual/hyperpolarization of the membrane = Inhibitory Post Synaptic Potential.
- ▶ An increased permeability to K^+ = hyperpolarization & stabilization of the membrane potential occurs.(IPSP)
- ▶ Potential changes associated with EPSP & IPSP = passive fluxes of ions down their concentration gradient.



4. Transmitter action on post junctional membrane

- ▶ The release transmitter combines with specific receptors on the post junctional membrane & depending on its nature induces an EPSP/IPSP.

EPSP

- ▶ Increase in permeability to all cations Na^+ / Ca^{++} influx through fast or slow channels causes depolarization followed by K^+ efflux.
- ▶ ionic movement is passive as the flow is down the concentration gradients.
- ▶ I. EPSP enhances muscle tone by activating voltage sensitive channels in smooth muscles, skeletal muscles & cardiac muscle by increasing the rate of spontaneous depolarization.
- ▶ II. EPSP initiates secretion through Ca^+ mobilization.



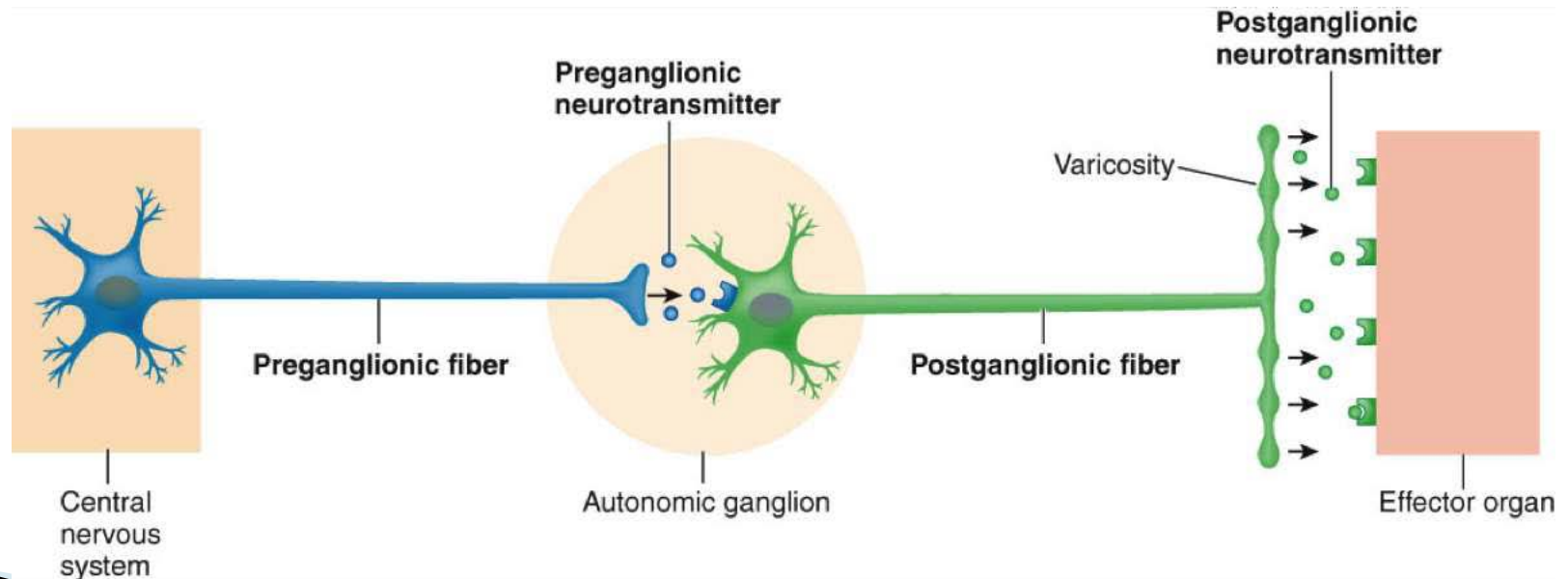
IPSP

- ▶ Increases in permeability to small ions like K^+ & Cl^- i.e., K^+ moves out & Cl^- moves in, in the direction of concentration gradient resulting in hyperpolarization.
- ▶ IPSP found in neurons & smooth muscles which tends to oppose excitatory potentials similarly initiated by other neuronal sources.
- ▶ Whether a propagated impulse or other response ensues depend on the summation of all potentials.



5. Destruction/dissipation of the transmitter

- ▶ Following the impulse transmission at junction (frequencies upto several 100/sec) it is obvious that there should be an efficient means of disposing of the transmitter following each impulse.



- ▶ **Locally degraded – Ach.**
- ▶ At cholinergic synapses = inhibition of AchE removal of the transmitter is accomplished principally by diffusion & the effect of the released Ach are potentiated & prolonged i.e., the transmitter Ach is locally degraded.
- ▶ **Reuptake by axonal terminal – NE**
- ▶ At adrenergic synapses = rapid termination of NE occurs by combination of simple diffusion & reuptake by the axonal terminals of most released norepinephrine.
- ▶ eg: NET, DAT, SERT.



6. Non electrogenic functions

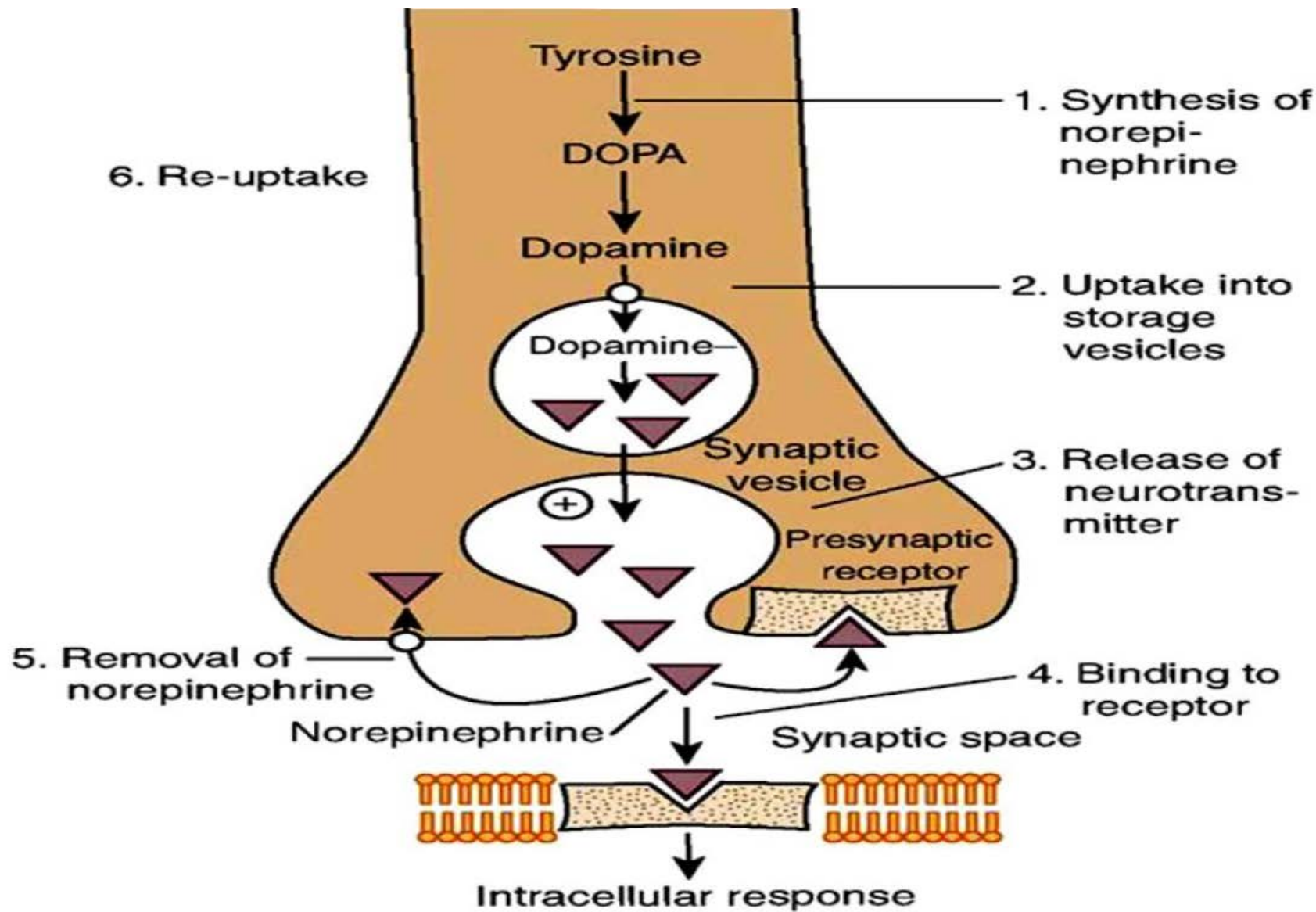
- ▶ The continual quantal release of NT's in amounts insufficient to elicit a post junctional response probably is important in the transjunctional control of NT action.
- ▶ The activity & turnover of enzymes involved in the synthesis & inactivation of NT's , the density of presynaptic & post synaptic receptors and other characteristics of synapses probably are controlled by trophic action of NT's or other trophic factors by the neurons or the target cells.



Adrenergic neurotransmission

- ▶ Transmission is restricted to the sympathetic division of ANS & conducted mainly by 3 closely related catecholamines
- ▶ i. Noradrenaline/norepinephrine – sympathetic post ganglionic nerve fibre except sweat glands, hair follicle, blood vessels, certain area of brain.
- ▶ ii. Adrenaline/epinephrine – adrenal medulla, chromaffin cells.
- ▶ iii. Dopamine – basal ganglia, limbic system CTZ, anterior pituitary in CNS.





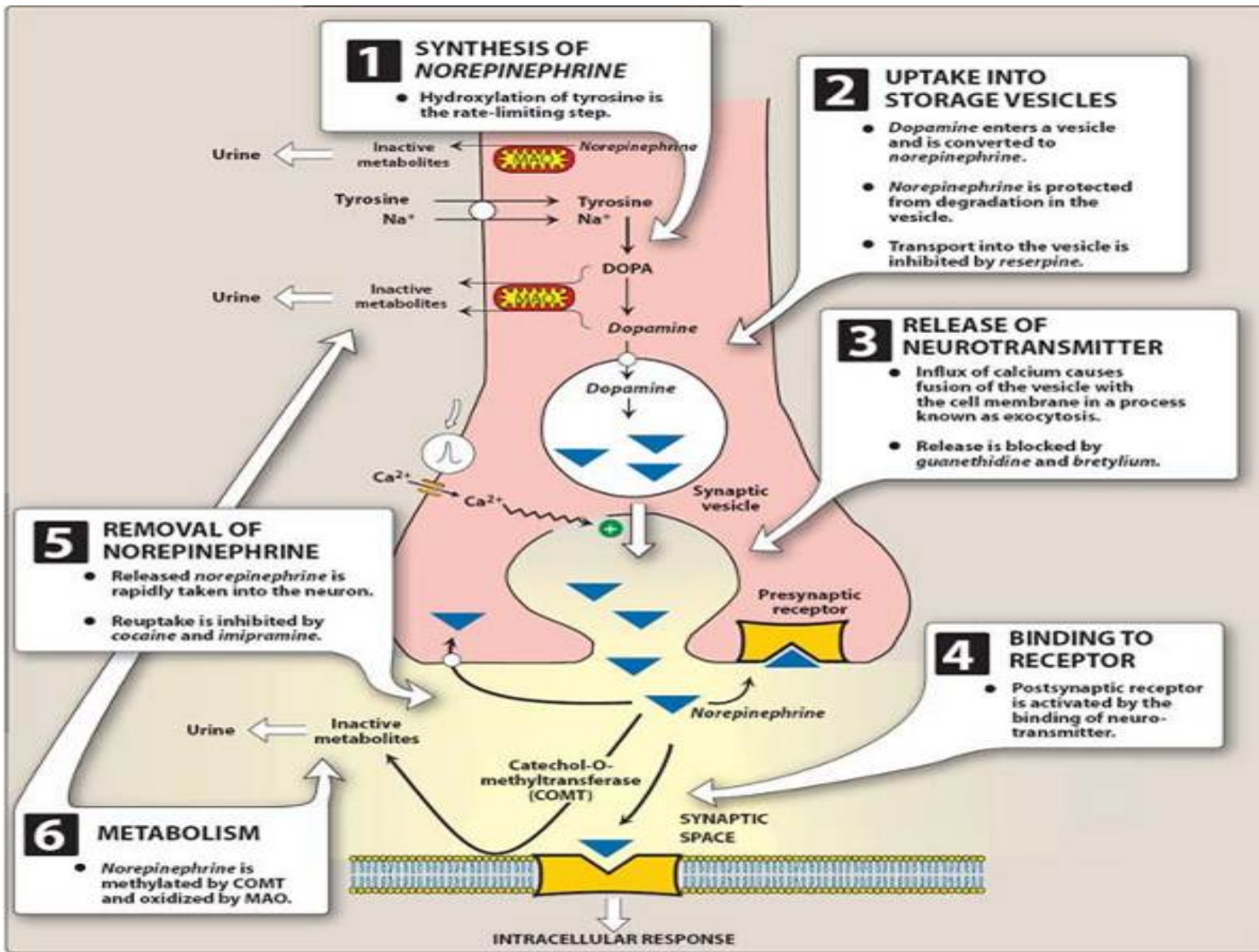
Biosynthesis of catecholamines

- ▶ Synthesized from the amino acid phenylalanine(liver)
- ▶ Hydroxylated by enzyme phenylalanine hydroxylase to yield tyrosine.
- ▶ Tyrosine is converted to dihydroxyphenylalanine DOPA by enzyme tyrosine hydroxylase*(rate limiting enzyme) & is inhibited by alpha methyl p tyrosine results in depletion of endogenous catecholamines
- ▶ DOPA is decarboxylated by enzyme dopa decarboxylase to Dopamine
- ▶ Dopamine is taken up in storage vesicle



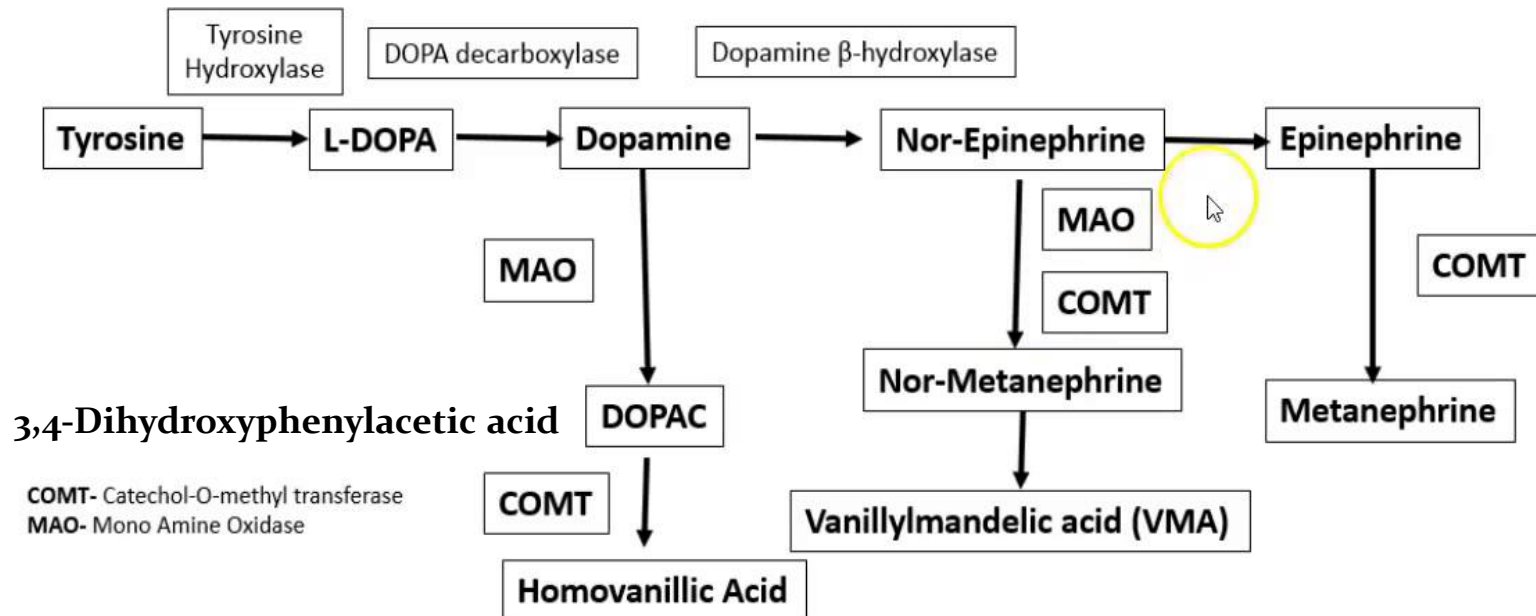
- ▶ In peripheral adrenergic neurons/adrenal chromaffin cells intra-granular dopamine is hydroxylated in the beta position of aliphatic side chain by dopamine beta hydroxylase to form NOREPINEPHRINE (NE)
- ▶ In adrenal medulla NE released from the granules of chromaffin cells & is N methylated with in the cytoplasm by **phenylethanolamine-n-methyltransferase** to form epinephrine
- ▶ Epinephrine is subsequently localized in intracellular storage granules prior to its release from adrenal medulla.





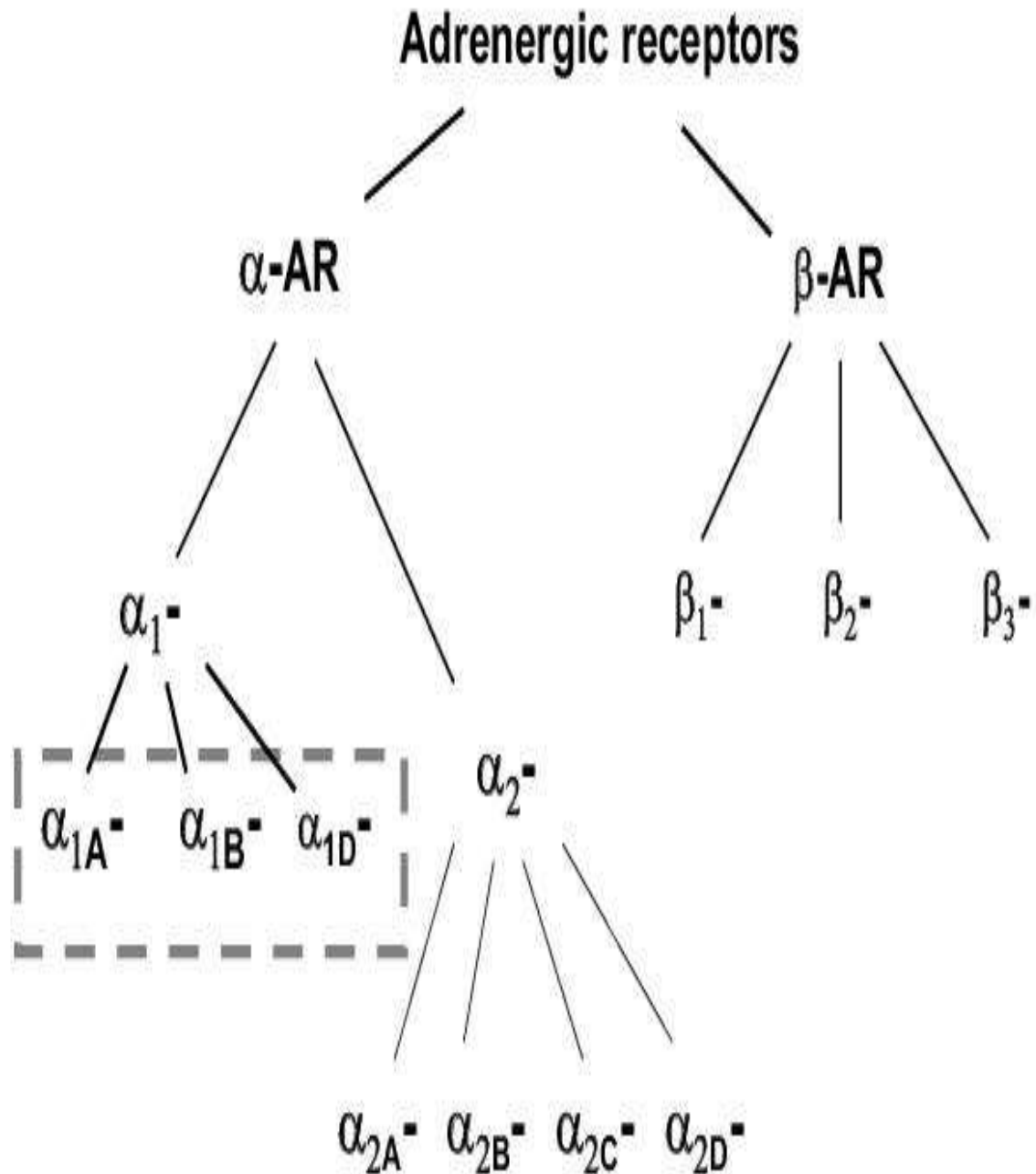
**Adrenergic Neurotransmission
and
Drugs affecting it**

Synthesis and Metabolism of Catechol amines



Adrenergic Receptors

- ▶ Membrane bound G protein coupled receptors
- ▶ Functions primarily by
- ▶ Increasing / decreasing the intracellular production of secondary messengers
- ▶ * cAMP
- ▶ * IP₃
- ▶ * DAG



CLASSIFICATIONS

	ALPHA RECEPTORS	BETA RECEPTORS
Rank order of potency	Adr >>> NA > Iso	Iso >>> Adr > NA
Antagonists	phenoxybenzamine	propranolol
Effector pathway	Increases IP3/ DAG Increases K ⁺ channel Decreases cAMP	Increases cAMP Increases Ca ⁺⁺ channel

Adr- Adrenaline
NA- Noradrenaline
Iso- Isoproterenol



	Beta1	Beta2	Beta3
Location	Heart Juxtaglomerular cells.	Bronchi, blood vessels, GIT, uterus, UT & eye.	Adipose tissue.
Selective agonist	Dabutamine	Salbutamol terbutaline	BRL 37344
Selective antagonist	Metaprolol Atenolol	Alpha methyl propranolol	CGP 20712A ICI 118551
Potency of NA as agonist	Strong	weak	strong

Cholinergic neurotransmission

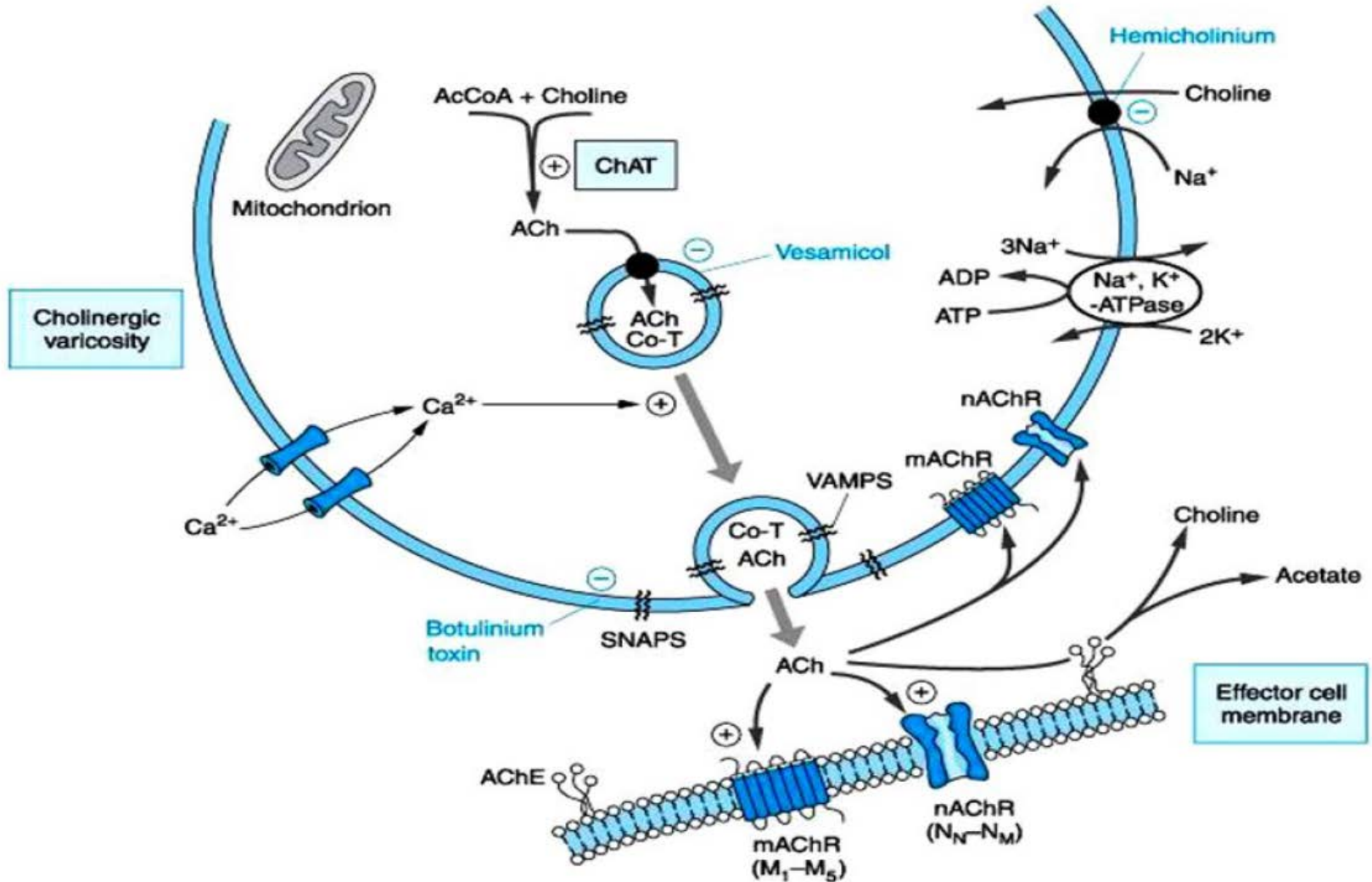
- ▶ Ach is the NT at most parasympathetic neuroeffector junction.
 - ▶ Autonomic ganglia, the adrenal medulla, somatic myoneural junctions & certain CNS regions.
 - ▶ Synthesis – Ach is synthesized locally in cholinergic nerve ending where ATP + Acetate + Coen-A combines initiating Acetate activating enzyme forming Acetyl CoEn – A
- (Choline+ Acetate) = acetylcholine + CoEn – A with enzyme choline acetyltransferase forming Acetylcholine chloride.



- ▶ Choline is actively taken up by the axonal membrane by Na^+ : Choline co-transporter & acetylated with the help of ATP and co-enzyme A by the enzyme choline acetyl transferase present in axoplasm.
- ▶ Hemicholinium – blocks choline uptake & depletes Ach
- ▶ Vesamicol – blocks the active transport of Ach into synaptic vesicles
- ▶ Botulinum toxin – inhibits release of Ach.
- ▶ Black widow spider toxin – induces massive release & depletion.



Cholinergic neurotransmission



Cholinergic receptors

- ▶ **Nicotinic receptors – ligand gated cation channels**

Occurs peripherally @ Neuroeffector junction, autonomic ganglia, adrenal medulla, & CNS where Ach is the NT.

all nicotinic receptors are selectively activated by Nicotine & blocked by either d – tubocurarine / Hexamoethonium.

- ▶ **Muscarinic receptors – G protein coupled receptors**

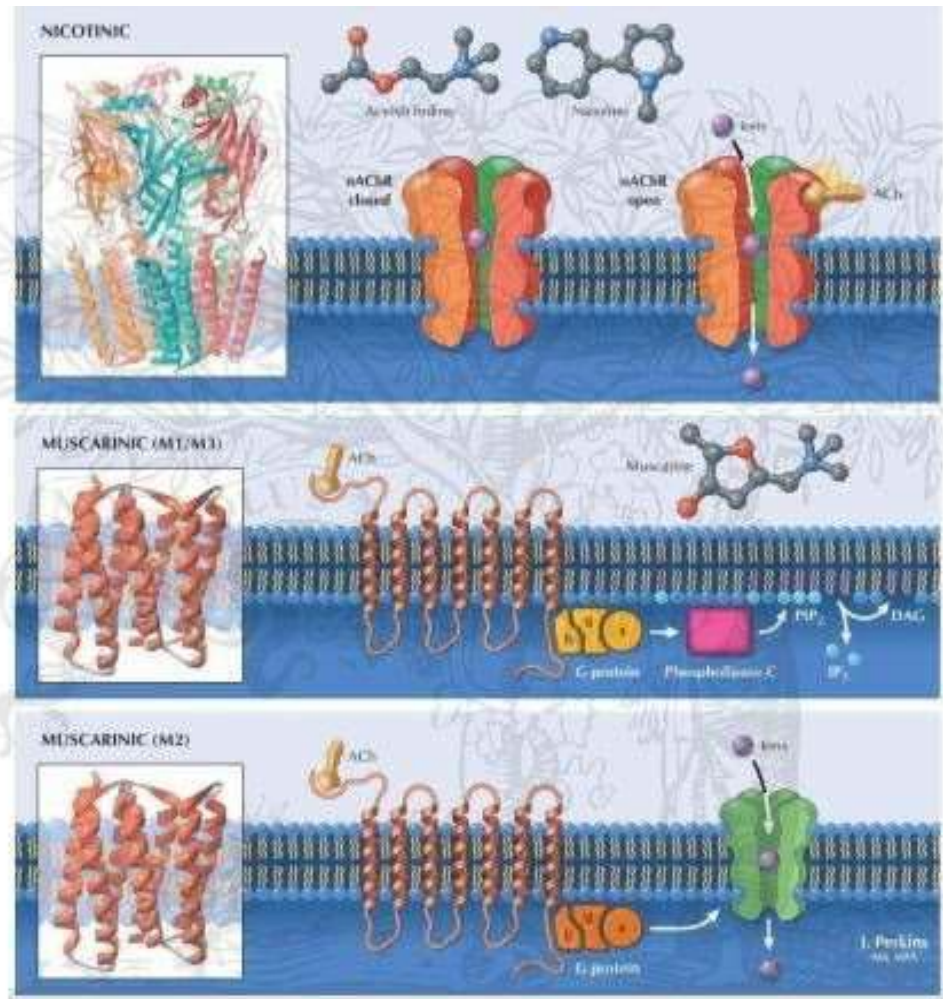
- ▶ Located primarily on autonomic effector cells in heart, smooth muscles & exocrine glands and certain areas of CNS.

- ▶ all blood vessels have muscarinic receptors although they lack cholinergic innervations.



Nicotinic & muscarinic receptors

- ▶ Nicotinic receptors conventionally divided into 2 types
 - Nm receptors
 - Nn receptors
- ▶ Muscarinic receptors divided into 5 sub types on the basis of molecular cloning i,e
 - ▶ M₁
 - ▶ M₂
 - ▶ M₃
 - ▶ M₄
 - ▶ M₅



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Comparison between Nm & Nn nicotinic receptors

N (MUSCULAR)

- ❑ skeletal muscle postjunctional
- ❑ structurally pentameric sub units
- ❑ MOA: opening of cation Na+ K+ channels results in depolarization.
- ❑ main function is contraction of skeletal muscle
- ❑ agonist – phenyl trimethyl ammonium
- ❑ Antagonist – d tubocurarine

N (NEURONAL)

Autonomic ganglia	Pre-junctional CNS	Post-junctional CNS
Opening of Na+K+channels- depolarization	Opening of Na+K+channels- depolarization	Opening of Ca++ channels -depolarisation
Transmission of impulse at autonomic ganglia, release of catecholamines from adrenal medulla	Excitation of CNS prejunctional control of transmitter release	Excitation of CNS postjunctional control of transmitter release
Agonist- DMPP	Agonist- Cystine	Agonist- Anatoxin A
Antagonist- Hexamethonium	Antagonist- mecamylamine	Antagonist- alpha bungarotoxin

M1 RECEPTOR	M ₂ RECEPTOR	M3 RECEPTOR	M4 RECEPTOR	M5 RECEPTOR
Autonomic ganglia, CNS, gastric glands, enteric nerves.	Heart, CNS, autonomic nerves.	Smooth muscle, CNS, exocrine glands	CNS	Present @ Low level in CNS & periphery
Gq/11	Gi/Go	Gq/11	Gi/Go	Gq/11
Increases IP3/DAG Increases cytosolic Ca ⁺⁺	Decreases cAMP Decreases Ca ⁺⁺ channel opening Increases K ⁺ channel	Increases IP3/DAG Increases cytosolic Ca ⁺⁺	Decreases cAMP Decreases Ca ⁺⁺ channel opening Increases K ⁺ channel	Increases IP3/DAG Increases cytosolic Ca ⁺⁺
Depolarisation in autonomic G, gastric secretion, CNS excitation, decrease dopamine release	Negative chronotropic & inotropic effects, Neuronal inhibition via autoreceptors, decreases ganglionic T	Sm Muscle contraction, glandular secretion, vasodilation via NO, inhibition of dopamine release	Inhibition of transmitter release in CNS & periphery, Increases dopamine release.	Dilation of cerebral vessels, facilitates dopamine release.
Agonist-XANOMELINE	METHACHOLINE	BETHANECHOL	XANOMELINE	
Antagonist-PIRENZEPINE	METHOCTRAMINE	DARIFENACIN		



SEROTONERGIC TRANSMISSION

- 5-hydroxy tryptamine occurs in the highest concentration in the following three organs.
 - 1) In the wall of intestine.
 - 2) In blood.
 - 3) In the CNS.

Biosynthesis:

- 1) tryptophan is converted into 5-hydroxytryptophan (in chromaffin cells and neurons but not in platelets) by the action of tryptophan hydroxylase.



2. It is then decarboxylated to 5-hydroxytryptamine by amino acid decarboxylase.

Platelets (& neurons) possess a high affinity for 5-HT uptake mechanism and become loaded with 5-HT as they pass through the intestinal circulation.

Serotonin stores in chromaffin cells and neurons as a cotransmitter with various peptide hormones such as somatostatin, substance P or vasoactive intestinal polypeptide(VIP).



Tryptophan



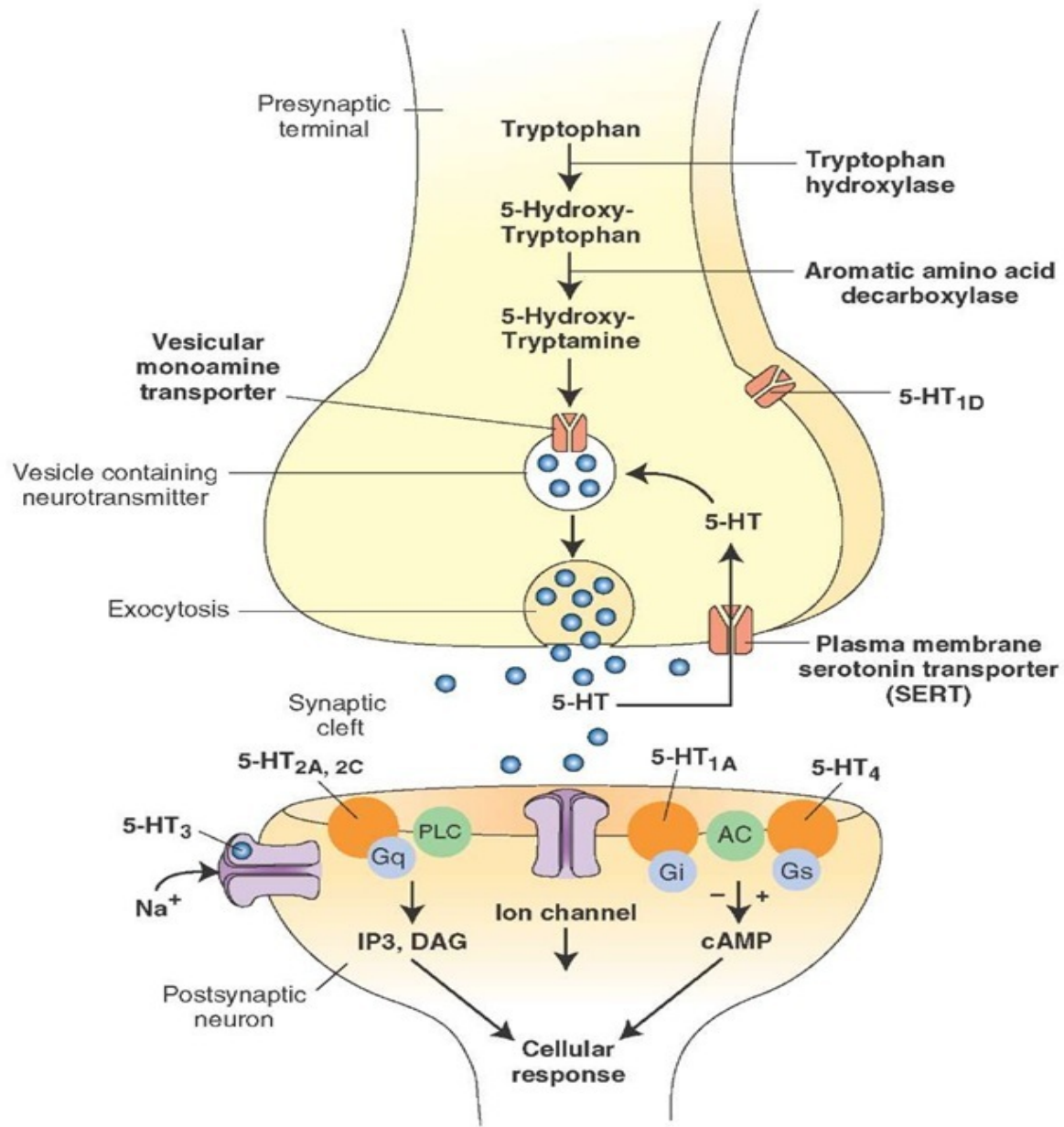
Tryptophan hydroxylase

5-Hydroxytryptophan (5-HTP)



Aromatic L-amino acid
decarboxylase

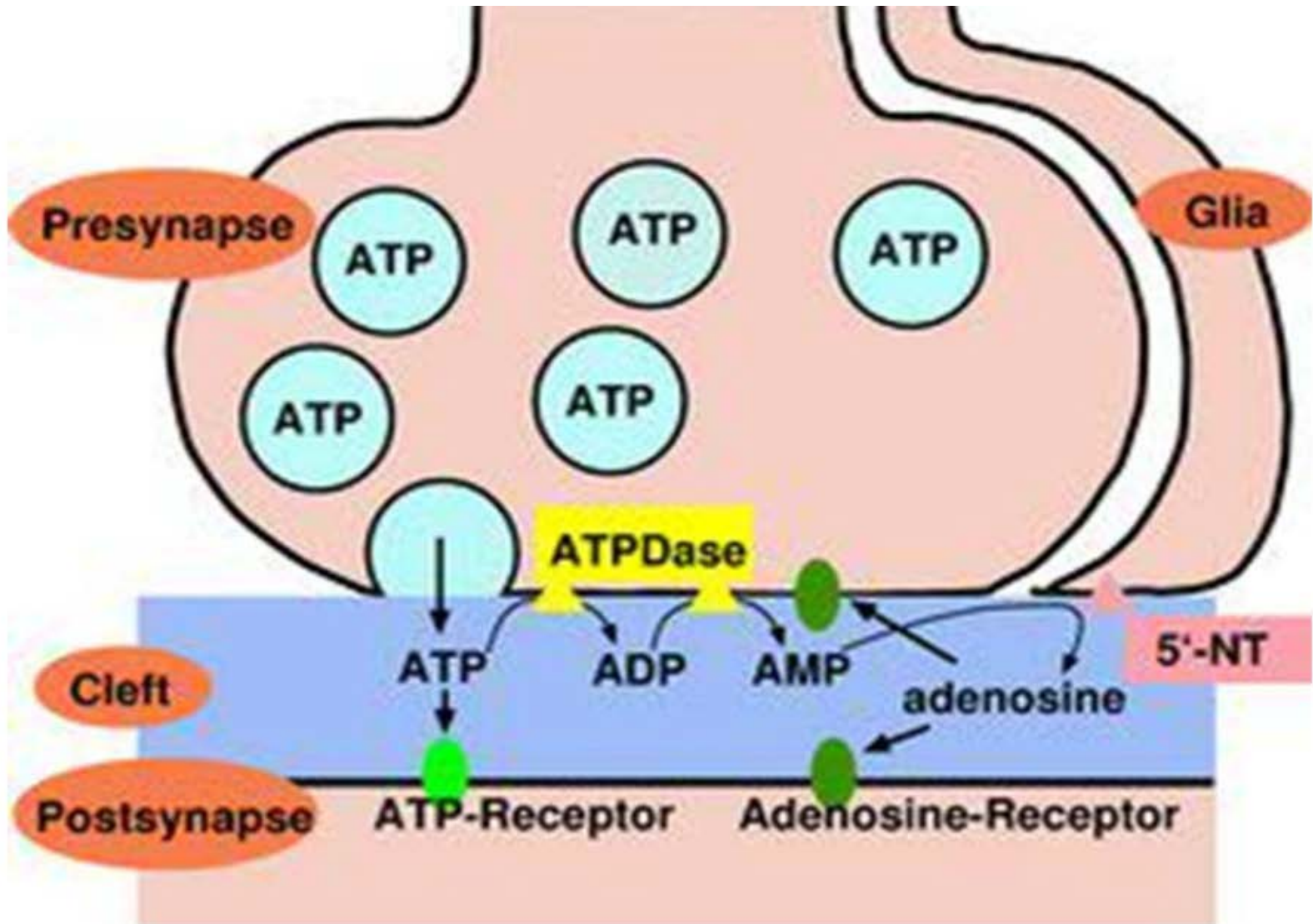
5-Hydroxytryptamine (5-HT; serotonin)



ATP AS NEUROTRANSMITTER

- ATP is a transmitter in the periphery both as a primary mediator and as a cotransmitter in noradrenergic nerve terminals.
- ATP is released on nerve stimulation in a calcium dependent manner, generally mimics the effects of nerve stimulation.
- ATP released from the cells is rapidly dephosphorylated by a range of nucleotidases into ADP and adenosine.
- Adenosine produced by hydrolysis of ATP exerts presynaptic inhibitory effects on the release of excitatory transmitters in CNS and periphery.





NON ADRENERGIC NON CHOLINERGIC NT'S

- ▶ Demonstrated in the autonomic innervation of the gut, vas deferens, urinary tract, salivary glands, blood vessels, where nerve stimulation is able to evoke limited response even in the presence of total adrenergic & cholinergic blockage.

On being release NANC transmitters serve to regulate

- ▶ Prejunctional/presynaptic release of primary NT's
- ▶ Postsynaptic sensitivity – neuromodulatory role
- ▶ serves as an alternative transmitter & exerts a tropic influence on the synaptic structure
- ▶ Eg: dopamine, enkephalins, somatostatin, VIP, NYP, ATP, PG's, NO, GABA & substance P



Putative neurohumoral substances

- ▶ Biological substances other than Ach & the catecholamines have been proposed as probable putative NT substances.
- ▶ **Histamine** – present at certain peripheral & CNS site as neuropeptide substances
- ▶ **Serotonin** – acts as NT` s in specific brain centers & peripheral nerves.
- ▶ serotonin (5HT) participates thermoregulation, sleep cycles, extrapyramidal influences on motor control of skeletal muscle.
- ▶ **GABA** – as inhibitory NT` s at certain CNS sites.

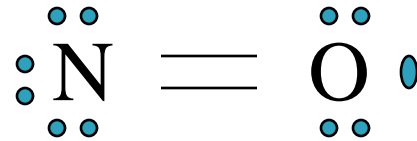


Nitric oxide

- ▶ Small & simple molecule with single atom of nitrogen & oxygen.
- ▶ With an unpaired electron in its outer orbit, NO is a radical species with biological half life of only few seconds.
- ▶ NO reacts rapidly with O₂ & with iron moiety of heme containing proteins.
- ▶ NO combustion product generated in cigarette smoke & jet engine exhaust.
- ▶ Relative to vascular effects.
- ▶ Mammalian cells can synthesize Nitric Oxide.



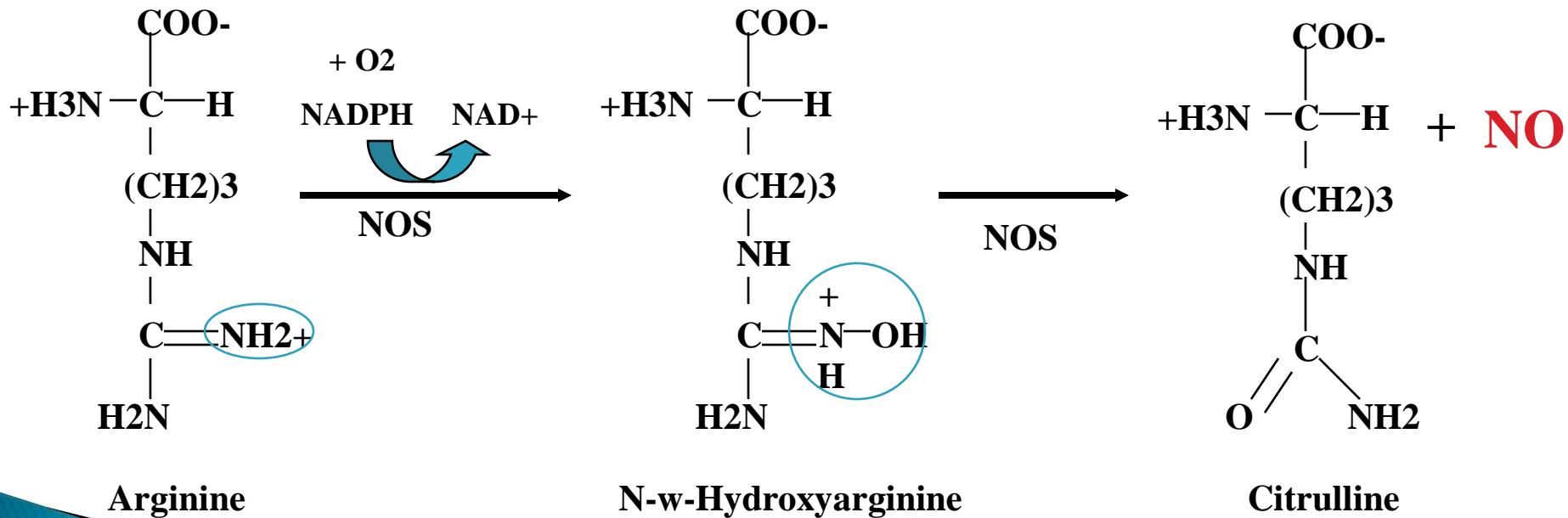
The structure and nature of Nitric Oxide

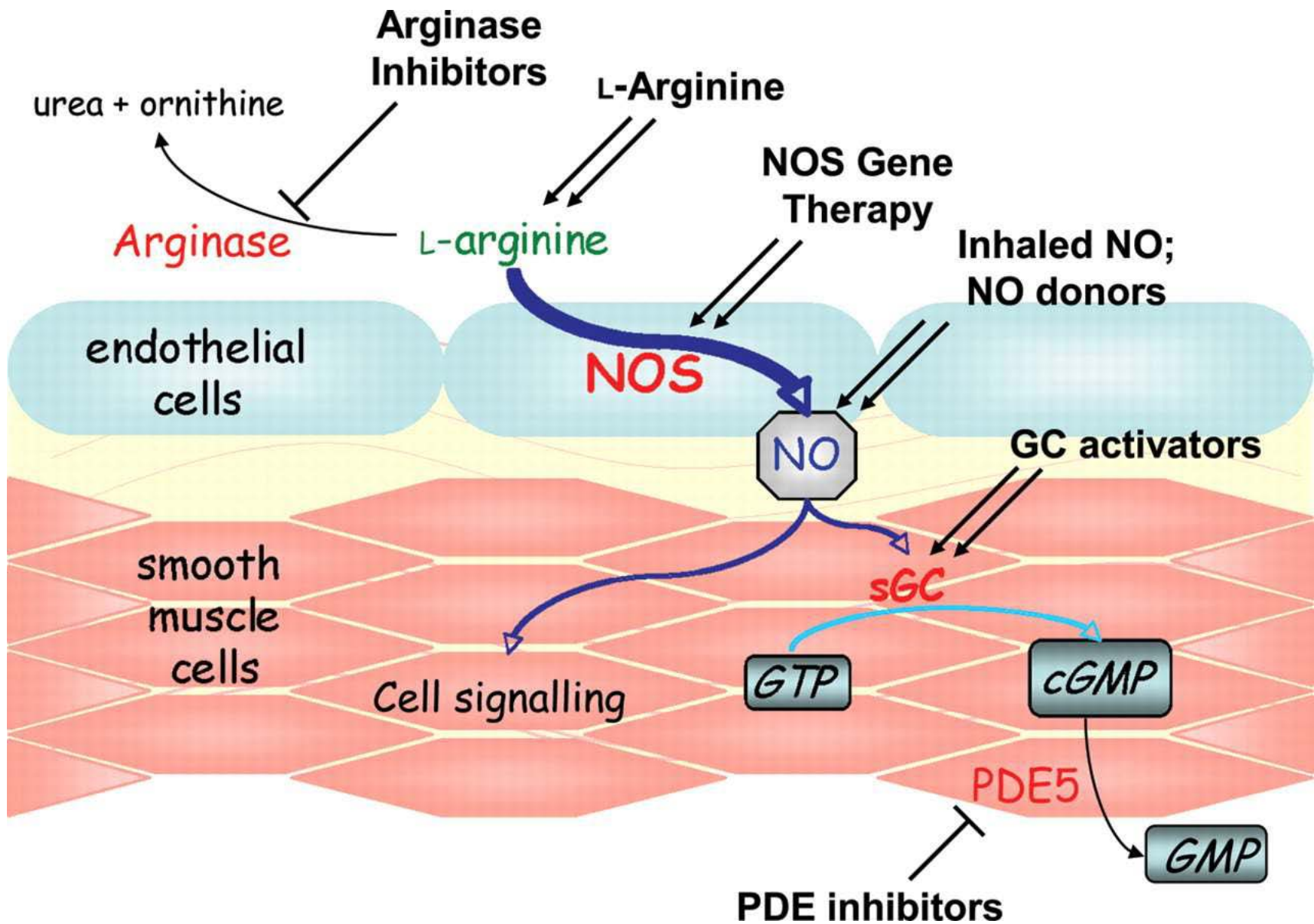


- ⌘ Nitric oxide is a diatomic free radical consisting of one atom of nitrogen and one atom of oxygen
- ⌘ Lipid soluble and very small for easy passage between cell membranes
- ⌘ Short lived, usually degraded or reacted within a few seconds
- ⌘ The natural form is a gas

Synthesis of Nitric Oxide

- ⌘ Nitric oxide is synthesized from L-arginine
- ⌘ This reaction is catalyzed by nitric oxide synthase, a 1,294 aa enzyme





Key roles by NO in bodily functions

- ▶ Immunomodulation
- ▶ Neurotransmitter in both CNS & ANS
- ▶ Cardio vascular dynamics
- ▶ Respiration
- ▶ Antimicrobial defenses
- ▶ Tumoricidal activity
- ▶ Intestinal peristalsis
- ▶ Penile erection



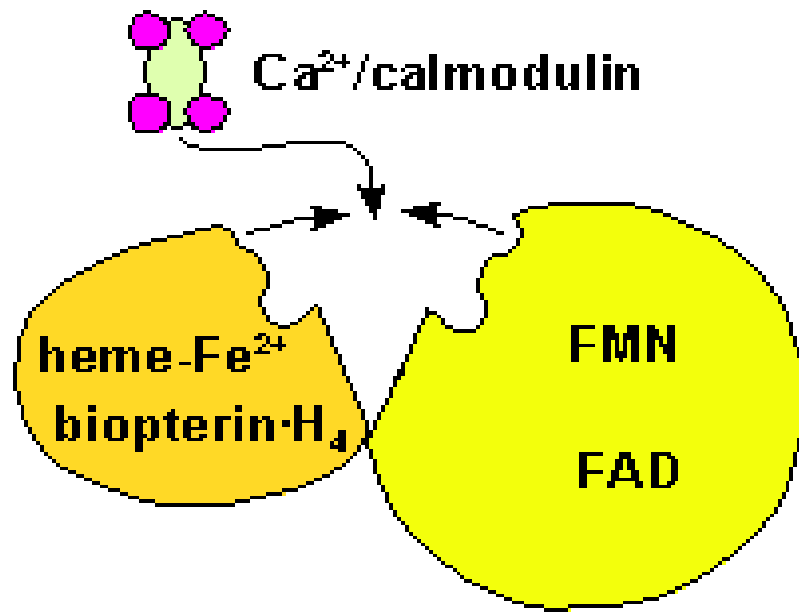
Activation of NOS

- ⌘ Glutamate neurotransmitter binds to NMDA receptors
- ⌘ Ca^{++} channels open causing Ca influx into cell
- ⌘ Activation of calmodulin, which activates NOS
- ⌘ Mechanism for start of synthesis dependent on body system
- ⌘ NO synthesis takes place in endothelial cells, lung cells, and neuronal cells

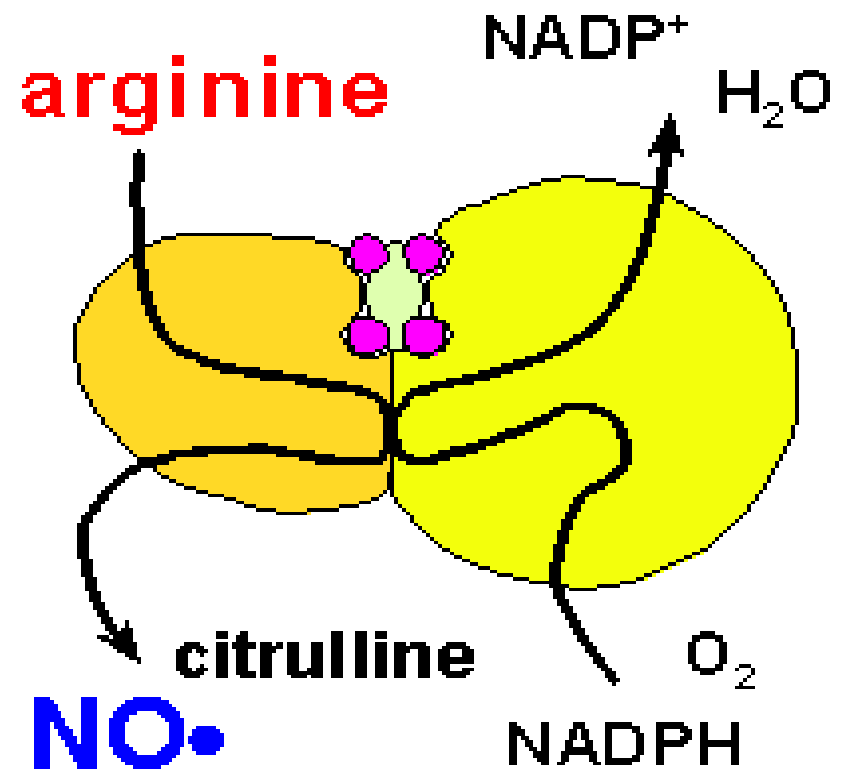


Nitric Oxide Synthase (NOS)

substrates, cofactors, and overall reaction



NOS catalyzes one of the most complex single-enzyme reactions in human biochemistry.



modified from Griffith and Stuehr (1995)

Types of NOS

⌘ NOS I

- ☒ Central and peripheral neuronal cells
- ☒ Ca^{+2} dependent, used for neuronal communication

⌘ NOS II

- ☒ Most nucleated cells, particularly macrophages
- ☒ Independent of intracellular Ca^{+2}
- ☒ Inducible in presence of inflammatory cytokines

⌘ NOS III

- ☒ Vascular endothelial cells
- ☒ Ca^{+2} dependent
- ☒ Vascular regulation

Nitric Oxide in the Nervous System

⌘ Nitric oxide as a neurotransmitter

- ☑ NO is a signaling molecule, but not necessarily a neurotransmitter
- ☑ NO signals inhibition of smooth muscle contraction, adaptive relaxation, and localized vasodilation

⌘ Nitric oxide believed to play a role in long term memory

- ☑ Memory mechanism proposed is a retrograde messenger that facilitates long term potentiation of neurons (memory)
- ☑ Synthesis mechanism involving Ca/Calmodulin activates NOS-I
- ☑ NO travels from postsynaptic neuron back to presynaptic neuron which activates guanylyl cyclase, the enzyme that catalyzes cGMP production
- ☑ This starts a cycle of nerve action potentials driven by NO



Is Nitric Oxide a “neurotransmitter?”

- ⌘ NO serves in the body as a neurotransmitter, but there are definite differences between other neurotransmitters used commonly in the body
 - ☒ NO is synthesized on demand vs. constant synthesis
 - ☒ NO diffuses out of the cells making it vs. storage in vesicles and release by exocytosis
 - ☒ NO does not bind to surface receptors, but instead exits cytoplasm, enters the target cell, and binds with intracellular guanylyl cyclase

- ⌘ Similarities to normal NTs
 - ☒ Present in presynaptic terminal
 - ☒ Natural removal from synaptic junction



Nitric Oxide in the Circulatory System

⌘ NO serves as a vasodilator

- ☒ Released in response to high blood flow rate and signaling molecules (Ach and bradykinin)
- ☒ Highly localized and effects are brief
- ☒ If NO synthesis is inhibited, blood pressure skyrockets
- ☒ (Diagram of vasodilation mechanism after muscular system)

⌘ NO aids in gas exchange between hemoglobin and cells

- ☒ Hemoglobin is a vasoconstrictor, Fe scavenges NO
- ☒ NO is protected by cysteine group when O₂ binds to hemoglobin
- ☒ During O₂ delivery, NO locally dilates blood vessels to aid in gas exchange
- ☒ Excess NO is picked up by HGB with CO₂

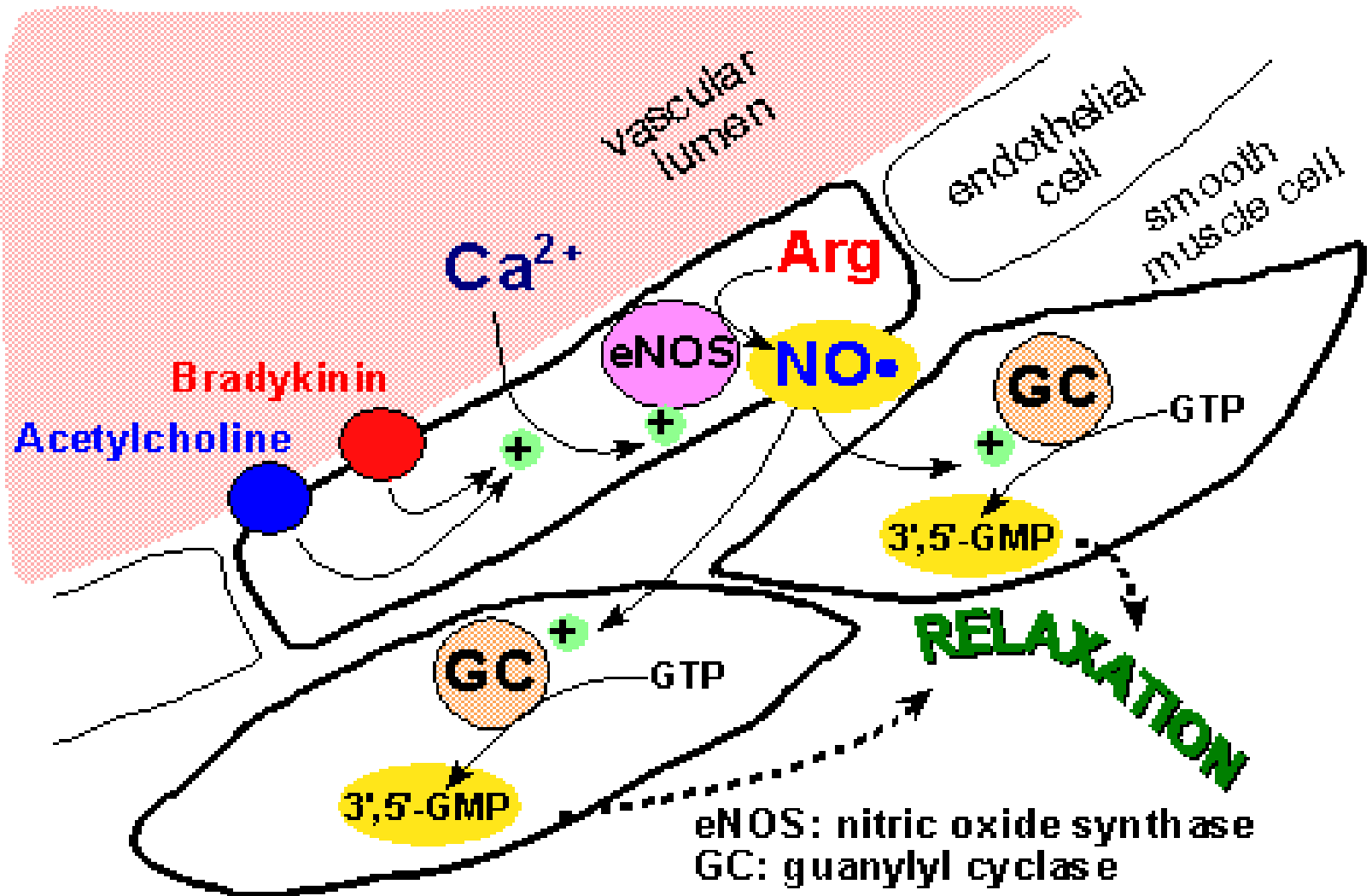


Nitric Oxide in the Muscular System

- ▶ NO was originally called EDRF (endothelium derived relaxation factor)
- ▶ NO signals inhibition of smooth muscle contraction
 - Ca^{+2} is released from the vascular lumen activating NOS
 - NO is synthesized from NOS III in vascular endothelial cells
 - This causes guanylyl cyclase to produce cGMP
 - A rise in cGMP causes Ca^{+2} pumps to be activated, thus reducing Ca^{+2} concentration in the cell
 - This causes muscle relaxation



Endothelium-dependent Vascular Relaxation



Nitric Oxide in the Immune System

- ▶ **NOS II catalyzes synthesis of NO used in host defense reactions**
 - Activation of NOS II is independent of Ca^{+2} in the cell
 - Synthesis of NO happens in most nucleated cells, particularly macrophages
 - NO is a potent inhibitor of viral replication
- ▶ **NO is a bactericidal agent**
 - NO is created from the nitrates extracted from food near the gums
 - This kills bacteria in the mouth that may be harmful to the body



Nitric Oxide in the Digestive System

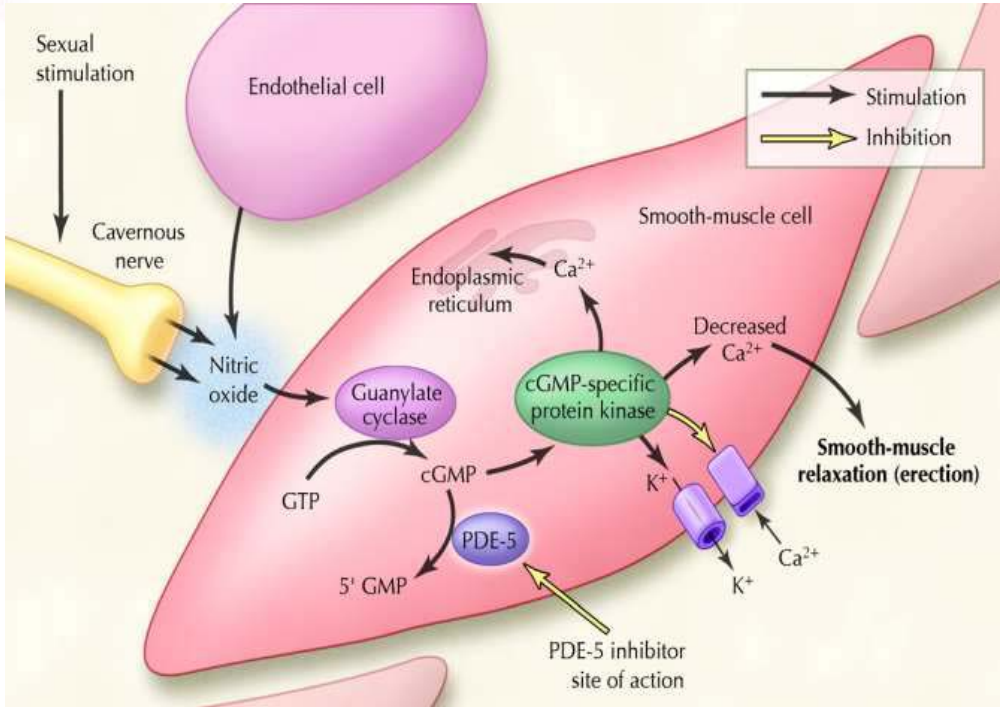
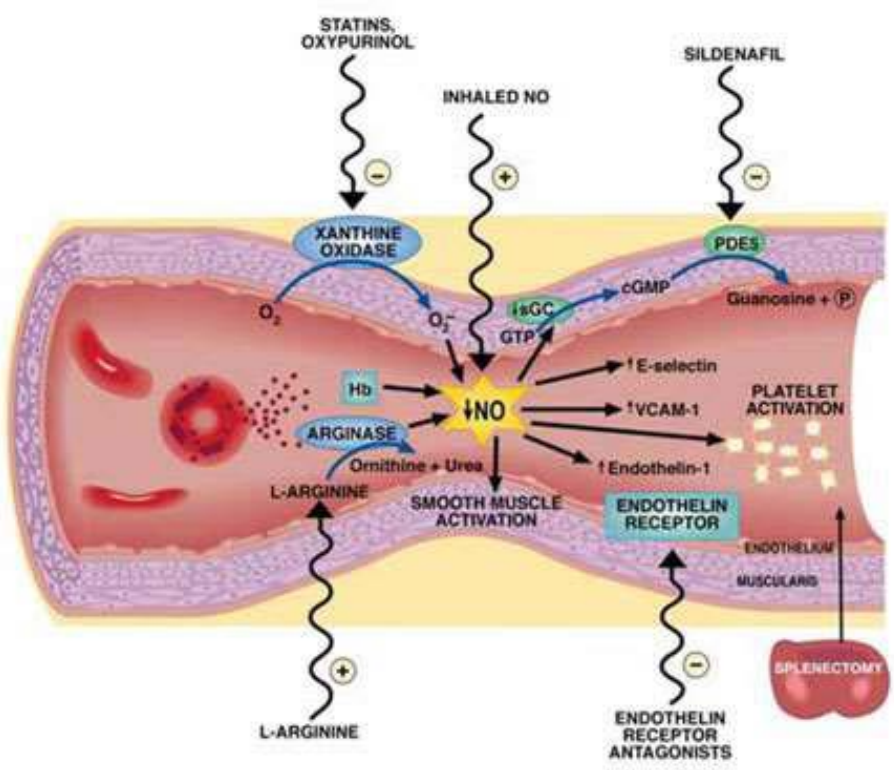
- ▶ **NO is used in adaptive relaxation**
 - NO promotes the stretching of the stomach in response to filling.
 - When the stomach gets full, stretch receptors trigger smooth muscle relaxation through NO releasing neurons



New research ideas involving Nitric Oxide

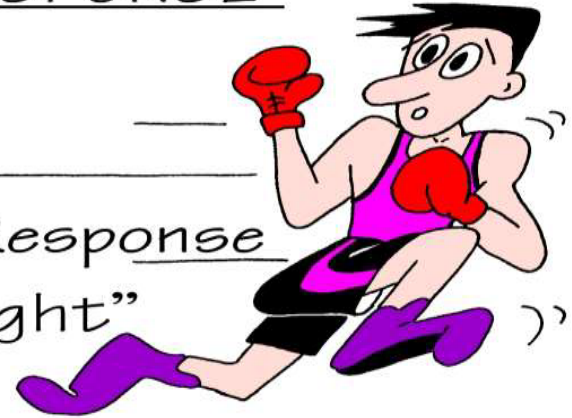
- ▶ The role NO might play in neuronal development
- ▶ The mechanism of NO inhibiting the different forms of NOS
- ▶ Diazeniumdiolates as NO releasing drugs
- ▶ Excessive NO release as the cause of most brain damage after stroke





“AUTONOMIC NERVOUS SYSTEM RESPONSE”

Sympathetic Response
“Fight or Flight”
(Stress)



Parasympathetic Response
“Rest & Digest”

THANK YOU

