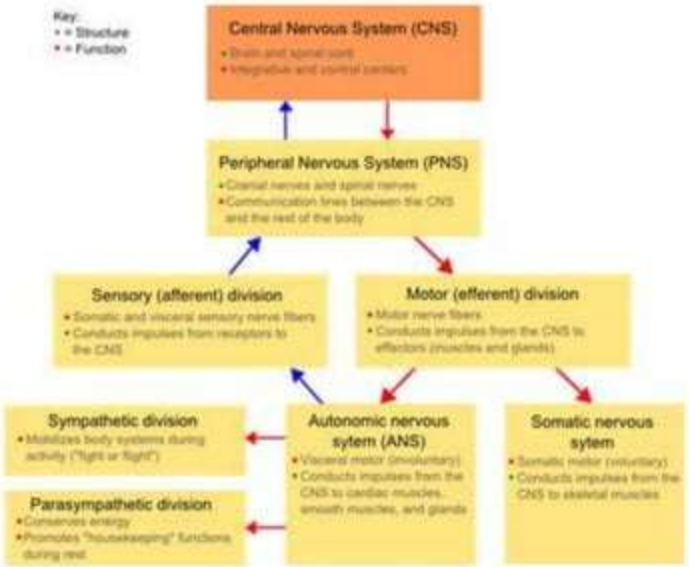
Anatomical and physiological consideration of Autonomic Nervous System

SAIFUDDIN PK

Msc,Pharmacolgy.PGIMER



Nervous system

FIGHT OR FLIGHT

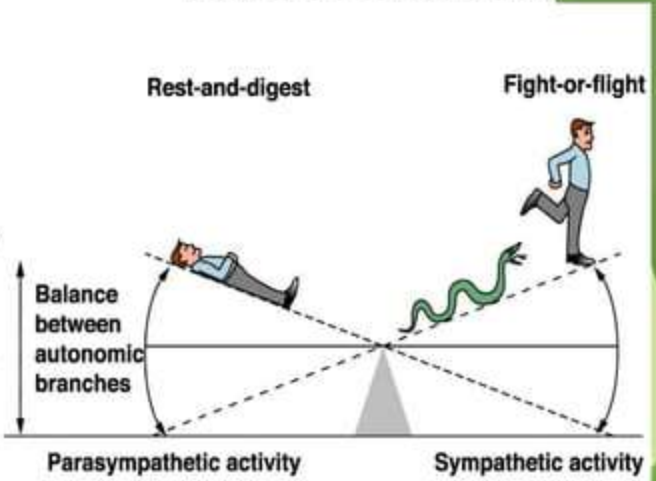
REST AND DIGEST

Introduction

- Autonomic nervous system is a part of peripheral nervous system that regulate involuntary physiologic process like
- Heart rate
- Blood pressure
- Respiration
- Digestion
- Sexual arousal
- It contains preganglionic neurone and post ganglionic neurone

- Often work in opposition
- Cooperate to fine-tune homeostasis
- Regulated by the brain; hypothalamus, pons and medulla
- Can also be regulated by *spinal reflexes*; no higher order input
- Pathways both consist of a two neuron system

Autonomic Nervous System

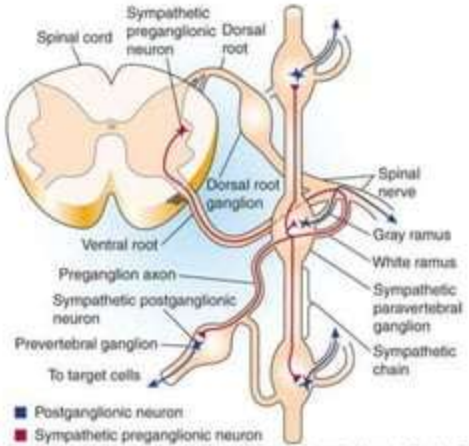


Preganglionic neuron (from CNS) → autonomic ganglion (outside CNS) → postganglionic neuron → target

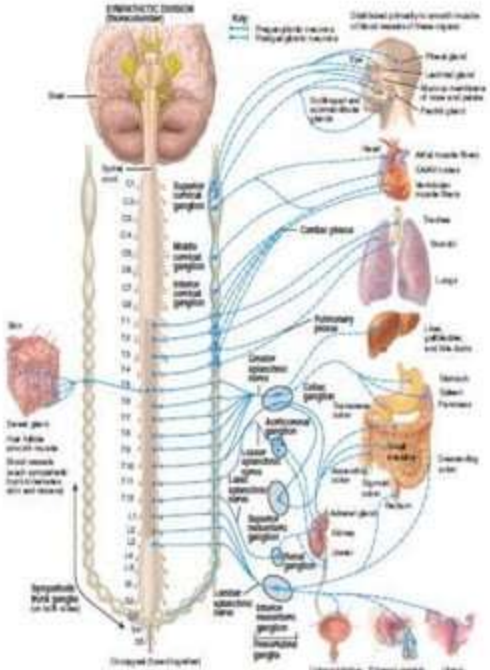
ANATOMY OF SNS

- LOCATION :T1 to L2(Thoraco Lumbar System)
- ORGIN : Inter Medio Lateral Columns of the spinal cord
- EXIT :Through Ventral roots of spinal cord
- COURSE :Through Sympathetic Ganglia
- paravertebral ganglion
  - Superier cervical ganglion
  - middle cervical ganglion
  - inferior cervical ganglion
- prevertebral ganglion
  - superior mesenteric ganglion
  - inferior mesenteric ganglion
  - celiac ganglion

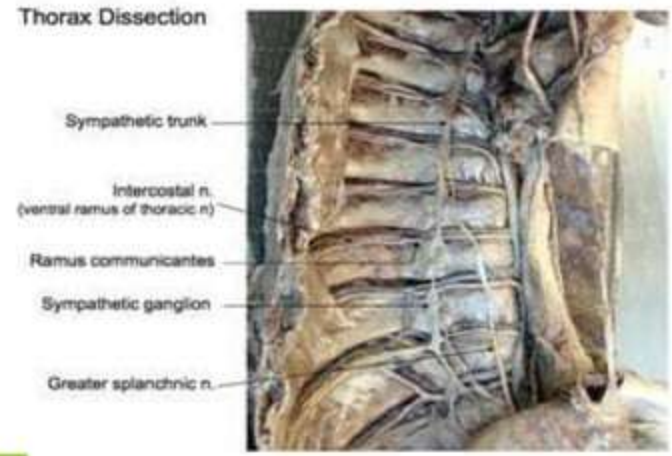
ANATOMY OF SYMPATHETIC NERVOUS SYSTEM



Source: Kim E. Barrett, Susan M. Barman, Scott Boitano, Heddwen L. Brooks: Ganong's Review of Medical Physiology, 25th Ed.
www.accessmedicine.com


SYMPATHETIC DIVISION
(Thoracolumbar)
Key
Preganglionic neurons
Postganglionic neurons
Distributed primarily to smooth muscle, cardiac muscle, or glands of these organs
Eye
Head
Lacrimal gland
Mucous membranes of nose and palate
Parotid gland
Sublingual and submandibular glands
Brain
Spinal cord
Heart
Cardiac plexus
Trachea
Bronchi
Lungs
Pulmonary plexus
Liver, gallbladder, and bile ducts
Skin
Sweat glands
Hair follicle arrector muscle
Blood vessels (each consisting of a vasoconstrictor fiber and vasodilator fiber)
Superior cervical ganglion
Middle cervical ganglion
Inferior cervical ganglion
Greater splanchnic nerve
Celiac ganglion
Stomach
Spleen
Pancreas
Adrenal gland
Kidney
Lesser splanchnic nerve
Aorticorenal ganglion
Least splanchnic nerve
Superior mesenteric ganglion
Small intestine
Ascending colon
Transverse colon
Descending colon
Sigmoid colon
Rectum
Renal ganglion
Ureter
Lumbar splanchnic nerve
Inferior mesenteric ganglion
Hypogastric nerve
Ganglia and plexuses
Urinary bladder
Internal genitalia

Sympathetic Trunk



ANATOMY OF PNS

- LOCATION :Cranio Sacral System
  Cranial Nerves (CN III, VII, IX, X)
  Sacral Nerves(2-4)
- ORGIN :Brain stem and Sacral segments

Parasympathetic fibers leave the brainstem by way of the following four cranial nerves.

1. **Oculomotor nerve (III).**

- Control the lens and pupil of the eye
- Preganglionic fibers enter the orbit and terminate in the ciliary ganglion behind the eyeball
- Postganglionic fibers enter the eyeball
- Innervate the ciliary muscle, which thickens the lens, and the pupillary constrictor, which narrows the pupil.

2. **Facial nerve (VII).**

- Regulate the tear glands, salivary glands, and nasal glands

3. Glossopharyngeal nerve (IX).

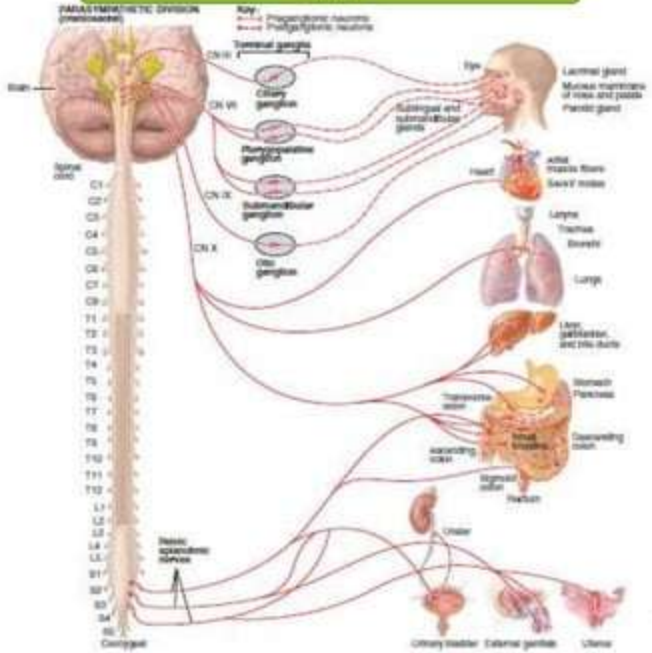
- Carries parasympathetic fibers concerned with salivation

4. Vagus nerve (X).

- Carries about 90% of all parasympathetic preganglionic fibers
- It travels down the neck and forms three networks in the mediastinum of the chest—the cardiac plexus, which supplies fibers to the heart; the pulmonary plexus, whose fibers accompany the bronchi and blood vessels into the lungs; and the esophageal plexus, whose fibers regulate swallowing.

NERVE	SUPPLY	ACTION
Occulomotor(III)	Iris and ciliary muscles of Eye	Constriction of pupil
Facial (VII)	Lacrimal,Sublingual and Submandibular ganglia	Salivation and lacrimation
Glossopharyngeal (IX)	Parotid salivary gland	Salivation
Vagus (X)	1)Dorsal nucleus:oesophagus,trachea,lungs,GI tract 2)Nucleus ambegius:Heart(SA,AV) Nucleus trachea,stomach,proximal colon 3)Nucleus solitarious:taste sensation 4)Spinal trigeminal:sensation from outer ear	↓ HR,↑ secretion
Sacral(S2,S3,S4)	Disatal colon,bladder,sex organs	Urination Erection

PNS


Brain
Spinal cord
CN III
CN VII
CN IX
CN X
Ciliary ganglion
Pterygopalatine ganglion
Submandibular ganglion
Otic ganglion
Eye
Lacrimal gland
Mucous membrane of nose and palate
Parotid gland
Sublingual and submandibular glands
Heart
Lungs
Trachea
Bronchi
Liver, gallbladder, and bile ducts
Stomach
Pancreas
Transverse colon
Ascending colon
Descending colon
Sigmoid colon
Rectum
Ureter
Urinary bladder
External genitals
Uterus
Coccygeal

PHYSIOLOGY OF PNS

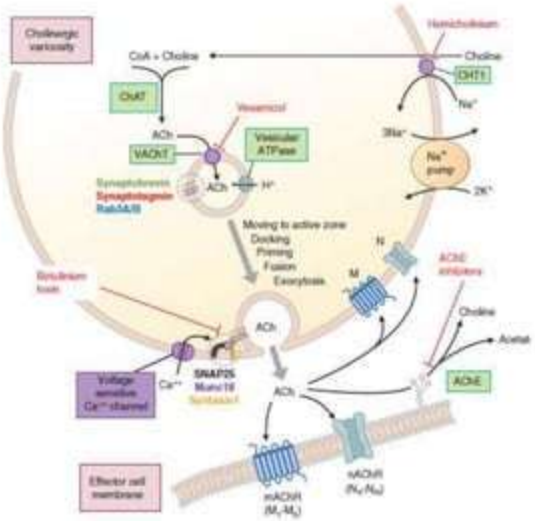
- NEUROTANSMITTER -ACETYLCHOLINE(Ach)

- Synthesis
- Storage
- Release
- Receptors

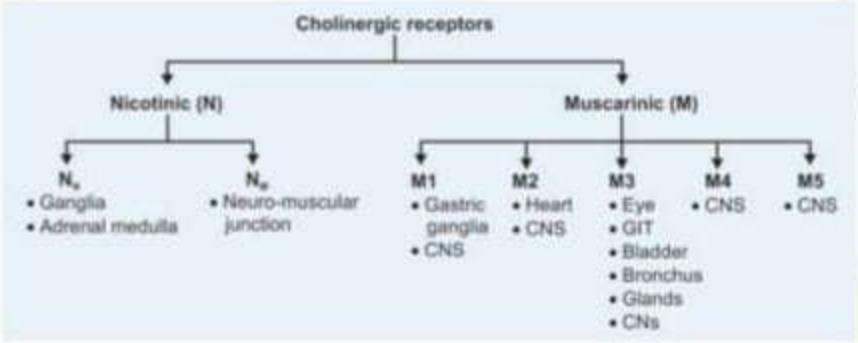
Synthesis of Ach

- Acetyl choline is synthesised by single step from choline and acetyl co enzyme A(Acetyl CoA) by the enzyme choline acetyl tranferase(ChAT)
- Acetyl Coenzyme A + Choline  Acetylcholine+Coenzyme A+H2O
- Uptake of choline by neurons is the rate limiting step in biosynthesis of Ach

Synthesis of Ach



Cholinergic receptors



Cholinergic receptors

Two types :Nicotinic and Muscarine receptors

1)Nicotinic receptors

- ligant gated ion channel and rapid in action
- Subdevided into

1. Muscle type(Nm)--- found in skeletal muscle where they mediate transmission at NMJ,blocked by D-tubocurare

2. Neuronal type(Nn)---found throughout the PNS,presynaptic.perisynaptic and post synaptic,CNS, adrenal medulla and non neuronal tissue(epithelial cells immune system).Bllocked by Hexamethonium

to date nine α (α 2- α 9) and three beta subunits genes are found.

Nicotinic receptors

RECEPTOR (Primary Receptor Subtype)*	MAIN SYNAPTIC LOCATION	MEMBRANE RESPONSE	MOLECULAR MECHANISM	AGONISTS	ANTAGONISTS
Skeletal Muscle (N_m) $(\alpha 1)_2\beta 1\varepsilon\delta$ adult $(\alpha 1)_2\beta 1\gamma\delta$ fetal	Skeletal neuromuscular junction (postjunctional)	Excitatory; end-plate depolarization; skeletal muscle contraction	Increased cation permeability (Na^+; K^+)	ACh Nicotine Succinylcholine	Atracurium Vecuronium *d*-Tubocurarine Pancuronium α-Conotoxin α-Bungarotoxin
Peripheral neuronal (N_n) $(\alpha 3)_2(\beta 4)_3$	Autonomic ganglia; adrenal medulla	Excitatory; depolarization; firing of postganglion neuron; depolarization and secretion of catecholamines	Increased cation permeability (Na^+; K^+)	ACh Nicotine Epibatidine Dimethylphenyl-piperazinium	Trimethaphan Mecamylamine
CNS neuronal $(\alpha 4)_2(\beta 4)_3$ *(α-BTX-insensitive)*	CNS; pre- and postjunctional	Pre- and postsynaptic excitation; prejunctional control of transmitter release	Increased cation permeability (Na^+; K^+)	Cytosine, epibatidine Anatoxin A	Mecamylamine DHβE Erysodine Lophotoxin
$(\alpha 7)_5$ *(α-BTX-sensitive)*	CNS; pre- and postsynaptic	Pre- and postsynaptic excitation; prejunctional control of transmitter release	Increased permeability (Ca^{2+})	Anatoxin A	Methyllycaconitine α-Bungarotoxin α-Conotoxin ImI

Cholinergic receptors Cntnd

2) Muscarine receptors- GPCR type receptors and slow action,Blocked by Atropine

subtypes:M1,M2,M3,M4,M5

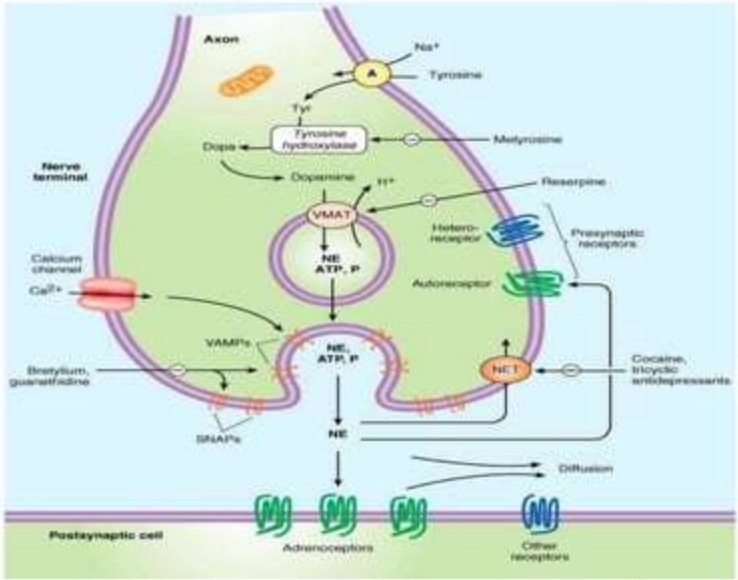
Receptor	Location	Function	Disease relavnce	Agonist	antagonist
M1	CNS, **Gastric** and salivary glands Autonomic ganglia	Cognitive function. ↓dopamine release ↑ in secretion	Alzheimers Cognitive dysfunction Schezophrena	Xanomeline	Pirenzepine Telenzepine
M2	**Cardiac**,smooth muscles.CNS Autonomic nerve terminals	Cardiac inhibition ↑contraction of smooth muscle	Cardiac dysfunction Pain,cognitive dysfunction.		Triptramine
M3	CNS,Eye Exocrine glands smooth muscles BV	↑secretion ↑contraction of bladder Blood vessel contraction	COPD Urinary incontnance IBD	Pilocarpine	Darifenacin
M4	CNS	Inhibtion of transmitter release in CNS and periphery.facilitation of DA release. Analgesia	Parkinsonism Neuropathic Pain		
M5	CNS Substantia nigra	regulate DA release. Augmentation of drug seeking behaviour	Parkinsonism Drug dependance		

SYMPATHETIC NERVOUS SYSTEM: Adrenergic transmission

- Norepinephrine-principal neurotransmitter
- Epinephrine
- Dopamine

Catecholamines

SYNTHESIS OF CATECHOLAMINES



Adrenergic receptors

- Adrenergic receptors are membrane bound **G-protein coupled receptors.**
- Adrenergic receptors are classified into two **types α and β.**
- The alpha-adrenergic receptors **α_1 receptor** (α_{1A}, α_{1B}, α_{1D}) and **α_2 receptor** (α_{2A}, α_{2B}, α_{2C}) are GPCRs.
- The beta-adrenergic receptors **β_1, β_2 and β_3** receptor are GPCRs.
- **Presynaptically located α_2 and β_2 receptors playing important roles in the regulation of neurotransmitter release from sympathetic nerve endings.**

Alpha adrenergic receptors subtypes

	G PROTEIN COUPLING	PRINCIPLE EFFECTORS	TISSUE LOCALIZATION	DOMINANT EFFECTS[a]
α_{1A}	$G\alpha_q$ ($\alpha_{11}/\alpha_{13}/\alpha_{14}$)	↑ PLC, ↑ PLA_2 ↑ Ca^{2+} channels ↑ Na^+/H^+ exchanger Modulation of K^+ channels ↑ MAPK Signaling	Heart, lung Liver Smooth muscle Blood vessels Vas deferens, prostate Cerebellum, cortex Hippocampus	• Dominant receptor for contraction of vascular smooth muscle • Promotes cardiac growth and structure • Vasoconstriction of large resistant arterioles in skeletal muscle
α_{1B}	$G\alpha_q$ ($\alpha_{11}/\alpha_{13}/\alpha_{14}$)	↑ PLC, ↑ PLA_2 ↑ Ca^{2+} channels ↑ Na^+/H^+ exchanger Modulation of K^+ channels ↑ MAPK signaling	Kidney, lung Spleen Blood vessels Cortex Brainstem	• Most abundant subtype in heart • Promotes cardiac growth and structure
α_{1D}	$G\alpha_q$ ($\alpha_{11}/\alpha_{13}/\alpha_{14}$)	↑ PLC, ↑ PLA_2 ↑ Ca^{2+} channels ↑ Na^+/H^+ exchanger Modulation of K^+ channels ↑ MAPK signaling	Platelets, aorta Coronary artery Prostate Cortex Hippocampus	• Dominant receptor for vasoconstriction in aorta and coronaries
α_{2A}	$G\alpha_i$ $G\alpha_o$ (α_{11}/α_{13})	↓ AC-cAMP-PKA pathway	Platelets Sympathetic neurons Autonomic ganglia Pancreas Coronary/CNS vessels Locus ceruleus Brainstem, spinal cord	• Dominant inhibitory receptor on sympathetic neurons • Vasoconstriction of precapillary vessels in skeletal muscle
α_{2B}	$G\alpha_i$ $G\alpha_o$ (α_{11}/α_{13})	↓ AC-cAMP-PKA pathway	Liver, kidney Blood vessels Coronary/CNS vessels Diencephalon Pancreas, platelets	• Dominant mediator of α_2 vasoconstriction
α_{2C}	$G\alpha_i$ ($\alpha_{11}/\alpha_{13}/\alpha_{14}$) $G\alpha_o$ (α_{11}/α_{13})	↓ AC-cAMP-PKA pathway	Basal ganglia Cortex, cerebellum Hippocampus	• Dominant receptor modulating DA neurotransmission • Dominant receptor inhibiting hormone release from adrenal medulla

Beta atrenergic receptors subtypes

	G PROTEIN COUPLING	PRINCIPLE EFFECTORS	TISSUE LOCALIZATION	DOMINANT EFFECTS
β_1	$G\alpha_s$	↑ AC-cAMP-PKA pathway ↑ L-type Ca^{2+} channels	Heart, kidney Adipocytes Skeletal muscle Olfactory nucleus Cortex, brainstem Cerebellar nuclei Spinal cord	• Dominant mediator of positive inotropic and chronotropic effects in heart
β_2	$G\alpha_s$	↑ AC-cAMP-PKA pathway ↑ Ca^{2+} channels	Heart, lung, kidney Blood vessels Bronchial smooth muscle GI smooth muscle Skeletal muscle Olfactory bulb Cortex, hippocampus	• Smooth muscle relaxation • Skeletal muscle hypertrophy
β_3	$G\alpha_s$	↑ AC-cAMP-PKA pathway ↑ Ca^{2+} channels	Adipose tissue GI tract, heart	• Metabolic effects

ADRENERGIC RECEPTORS AND DRUGS

Receptor Type	Tissue Distribution	Mechanism of Action	Agonist Potency	Physiological Effects	Agonist	Antagonist
α1	Vascular Smooth Muscles, Visceral smooth Muscles	Gq-protein coupled activates Phospholipase C, IP3+DAG	Epi ≥ NE >> Iso	Smooth muscle contractions, Gluconeogenesis, Vasoconstriction	Norepinephrine, Phenylephrine, Methoxamine	Doxazosin, Phentolamine, Prazosin
α2	Pre-synaptic terminals, pancreas, platelets, Ciliary epithelium, Salivary Glands	Gi-protein coupled inhibits Adenyl cyclase	Epi ≥ NE >>Iso	Inhibits release of Neurotransmitter	Clonidine, Monoxidine	Yohimbine, Idazoxan, Tolazoline
β1	Heart, Kidney, some pre-synaptic terminals	Gs-protein coupled activates Adenyl cyclase +PKA	Iso > Epi ≥ NE	Increase heart rate and Renin secretion	Isoproterenol, Norepinephrine, Dobutamine	Propranolol, Metoprolol, Atenolol
β2	Visceral smooth muscles, Bronchioles, Liver, Skeletal Muscles	Gs-protein coupled activates Adenyl cyclase +PKA, Ca-channels	Iso > Epi >> NE	Vasodilation, Bronchodilation, Inhibits insulin secretion	Isoproterenol, Salbutamol, Salmeterol, Albuterol, Formoterol, Terbutaline, Levalbuterol	Propranolol, ICI-118,551, Nadolol, Butoxamine
β3	Adipose Tissue	Gs-protein coupled activates Adenyl cyclase +PKA	Iso = NE > Epi	Increase lipolysis	Isoproterenol, Amibegron, Solabegron	SR59230A

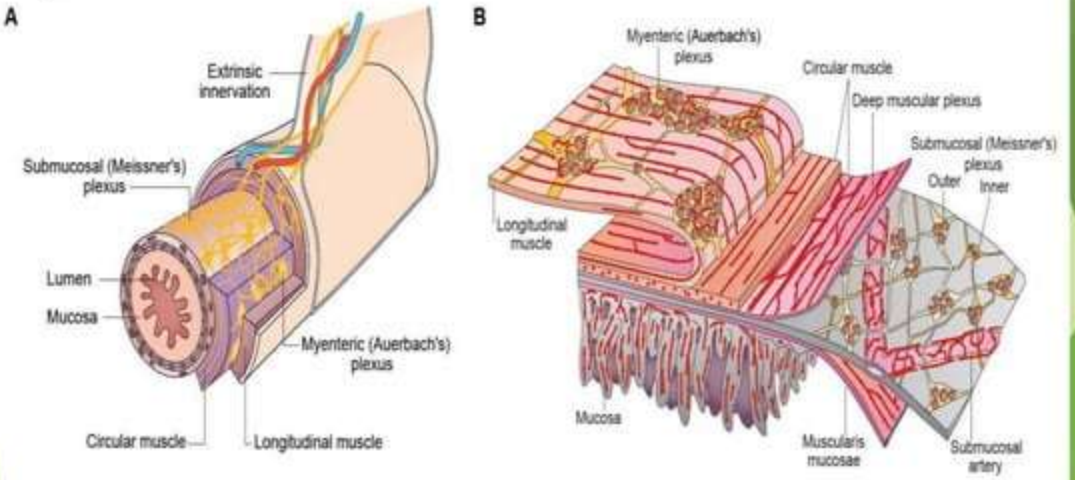
NE: Norepinephrine, **Epi:** Epinephrine and **Iso:** Isoproterenol

Enteric Nervous System

- The process of mixing,propulsion,and absorbtion of nutrients in the GI tract are controlled locally through the PNS called ENS
- ENS comprises the components of the SNS and PNS and sensory nerve
- These Interneurons network forms two plexus
- The Myenteric plexus located bw Longitudinal and Circular Muscles which plays an important role in contraction and relaxation of GI Muscles
- The Meissners Pluxes also known as submucosal pluxes involves the secretory and absorbtive function of the GI Epithelium
- Ach is the primery NT along with ATP,Substance P,and 5HT

ENTERIC NERVOUS SYSTEM

Figure 1



THANK YOU

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