Lecture Notes on

Drugs acting on Autonomic Nervous System

(Unit II)

[As per VCI MSVE 2016 Syllabus]

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Unit II

DRUGS ACTING ON AUTONOMIC NERVOUS SYSTEM

Syllabus

Chapter 1: Introduction to Autonomic Nervous System.

Chapter 2: Neurohumoral transmission. Pharmacology of neurotransmitters.

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Chapter 7: Adrenergic Drugs (Adrenoceptor agonists or Sympathomimetics).

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Chapter 9: Drugs acting on Autonomic Ganglia.

Chapter 10: Autacoids: Histamine, histamine analogues and antihistaminic agents, 5-Hydroxytryptamine and its agonists and antagonists, eicosanoids, platelet activating factors, angiotensin, bradykinin and kallidin.

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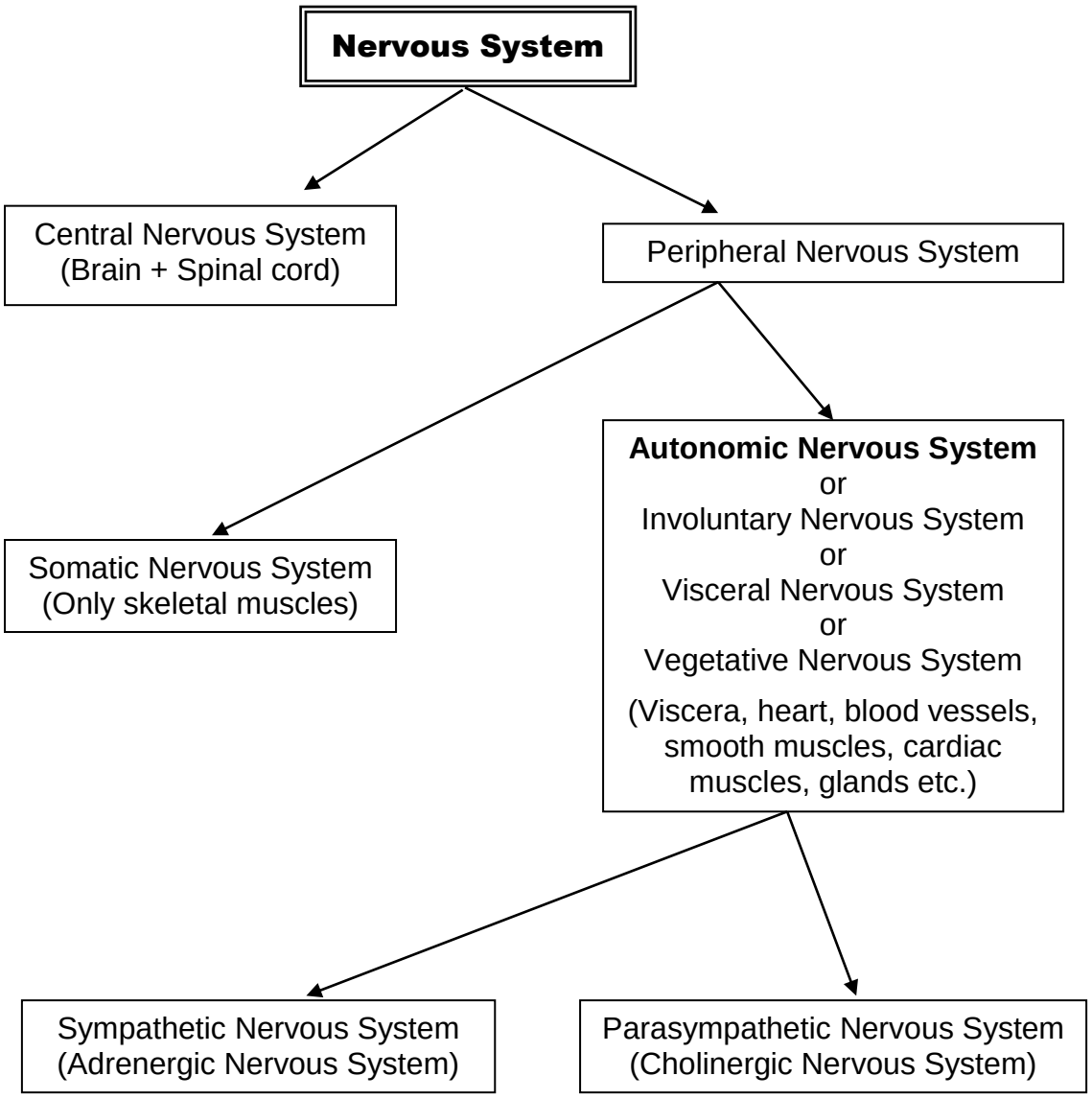
Suggested Text books of Pharmacology:

1. Veterinary Pharmacology & Therapeutics (10th Edn.-2018) – Jim E. Riviere and Mark G. Papich
2. Essentials of Medical Pharmacology (8th Edn.-2019) – K.D. Tripathi
3. Rang & Dale's Pharmacology (9th Edn.- 2019) – James M. Ritter, Rod Flower, Graeme Henderson, Yoon Kong Loke, David MacEwan & Humphrey P. Rang.
4. Goodman & Gilman's The Pharmacological Basis of Therapeutics (13th Edn.-2018) – Laurence L. Brunton, Randa Hilal-Dandan & Björn C. Knollmann.

Chapter - 1

Introduction to Autonomic Nervous System

INTRODUCTION TO THE AUTONOMIC NERVOUS SYSTEM



Terminology:

Afferent (Sensory): Nerves that convey flow of impulse from peripheral to CNS.

Efferent (Motor): Nerves that convey impulses from the brain and spinal cord (CNS) to muscles, glands and other effector organs.

Ganglion: It is an aggregation of synapses.

Neuroeffector junction: The junction of a post-ga1nglionic axonal terminal with its effector cell is termed a neuroeffector junction.

Nerve plexus: It is a network of nerve fibres.

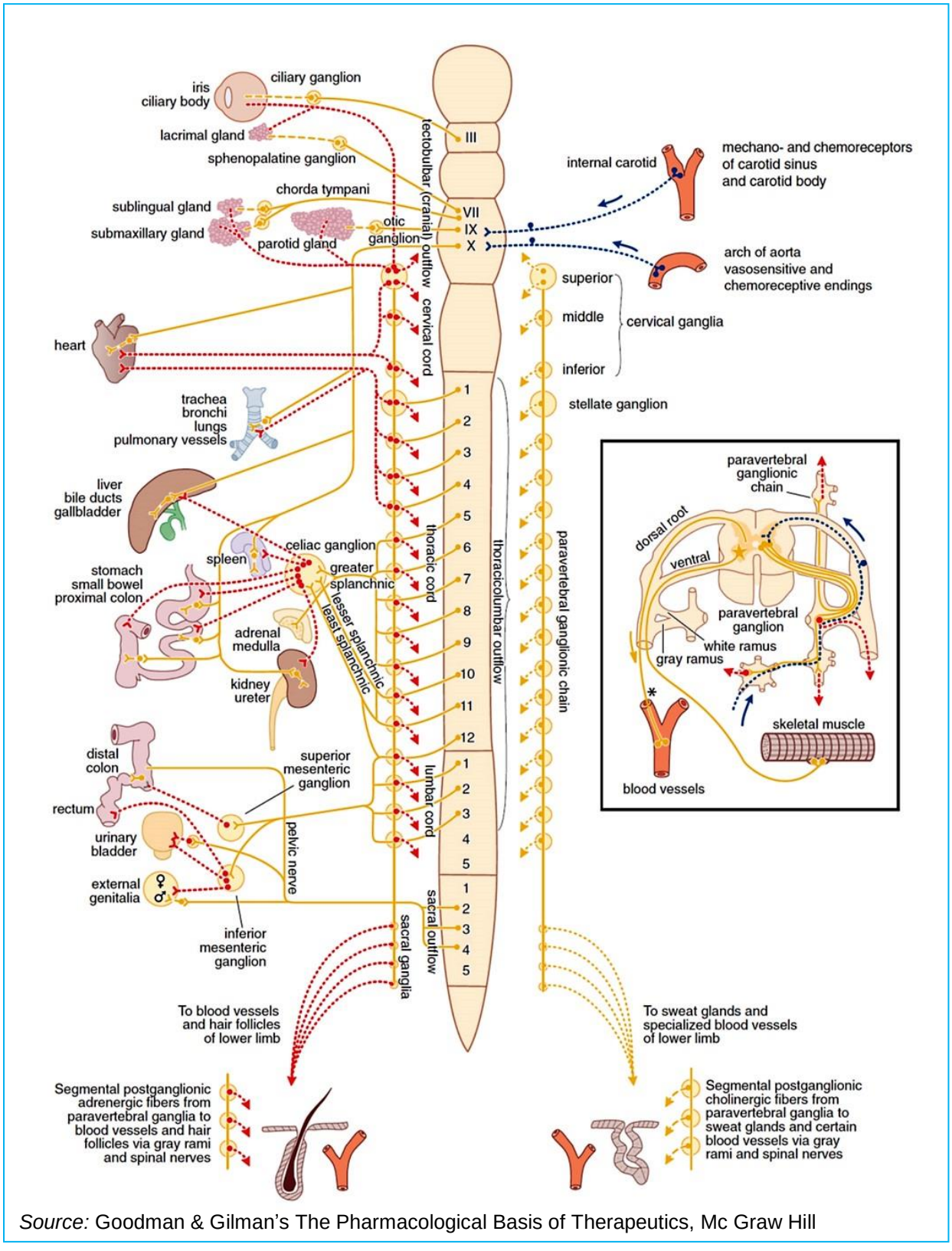
Autonomic nervous system (A.N.S.) is a peripheral complex of nerves, plexuses and ganglia that are organized to modulate the involuntary activity of the secretory glands, smooth muscles and visceral organs. This system functions to sustain homeostatic conditions during periods of reduced physical and emotional activity, and equally important, to assist in internal bodily reactions to stressful circumstances.

Nerves transmit their impulses across most synapses and neuroeffector junctions by means of specific chemicals called as neurohumoural transmitters or simply neurotransmitters.

The autonomic drugs exert their actions on smooth muscles, cardiac muscles, glands and visceral organs by mimicking or modifying the action of neurotransmitters released by autonomic fibres either at ganglia or at effector cells.

DIFFERENCES BETWEEN AUTONOMIC AND SOMATIC NERVOUS SYSTEM:

Autonomic Nervous System (A.N.S.)	Somatic Nervous System
(i) Efferent nerves of A.N.S. supply all innervated structures of the body except skeletal muscles.	(i) They supply skeletal muscles.
(ii) The most distal synaptic junction in A.N.S. occurs in ganglia that are entirely outside the cerebrospinal axis.	(ii) Somatic nerves contain no peripheral ganglia, and synapses are located entirely within the cerebrospinal axis.
(iii) Many autonomic fibres form extensive peripheral plexuses.	(iii) No peripheral plexus is present in somatic nerve fibres.
(iv) When cut, organ supplied generally show some level of spontaneous activity independent of intact innervations.	(iv) When cut, skeletal muscles supplied become paralyzed and undergo atrophy.
(v) Pre-ganglionic and post-ganglionic fibres are present.	(v) No such nomenclature.
(vi) Post-ganglionic autonomic nerve fibres are generally non-myelinated (slow conduction of impulse), whereas pre-ganglionic fibres are myelinated (fast conduction of nerve impulse).	(vi) Most fibres of skeletal muscles are myelinated.



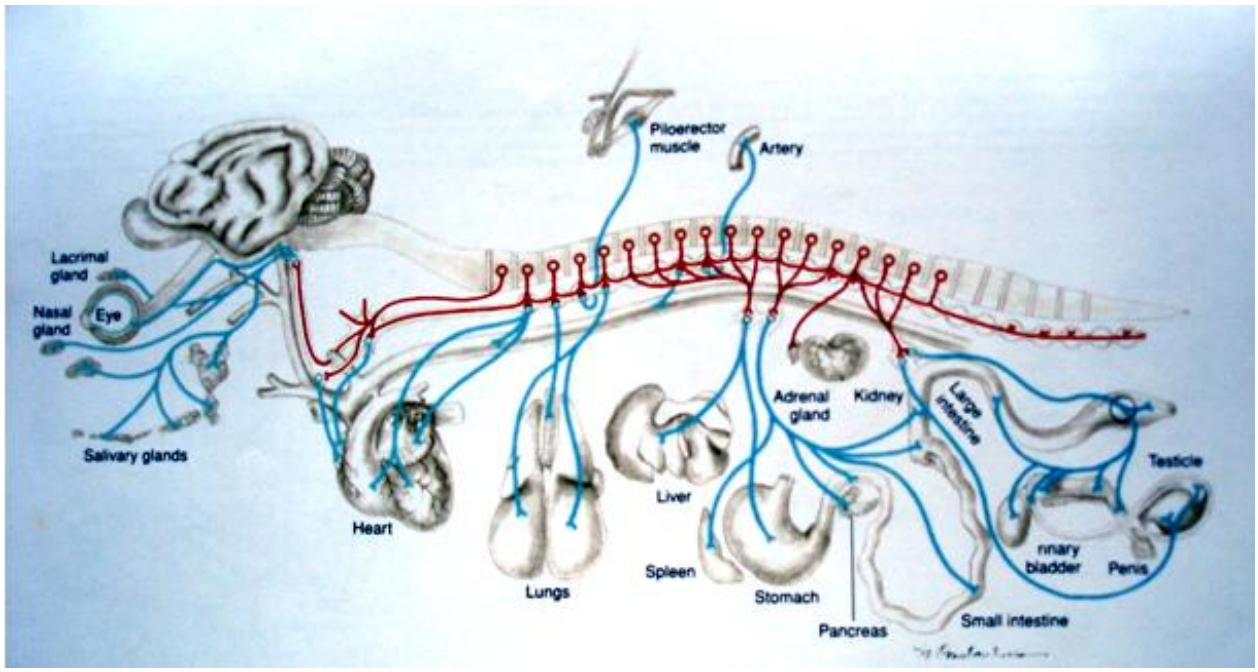
Source: Goodman & Gilman's The Pharmacological Basis of Therapeutics, Mc Graw Hill

Figure : ***The Autonomic Nervous System***

Schematic representation of the autonomic nerves and effector organs based on chemical mediation of nerve impulses. Yellow (——), cholinergic; red (——), adrenergic; dotted blue (– – – –), visceral afferent; solid lines, preganglionic; broken lines, postganglionic. The rectangle at right shows the finer details of the ramifications of adrenergic fibers at any one segment of the spinal cord, the path of the visceral afferent nerves, the cholinergic nature of somatic motor nerves to skeletal muscle, and the presumed cholinergic nature of the vasodilator fibers in the dorsal roots of the spinal nerves. The asterisk (*) indicates that it is not known whether these vasodilator fibers are motor or sensory or where their cell bodies are situated.

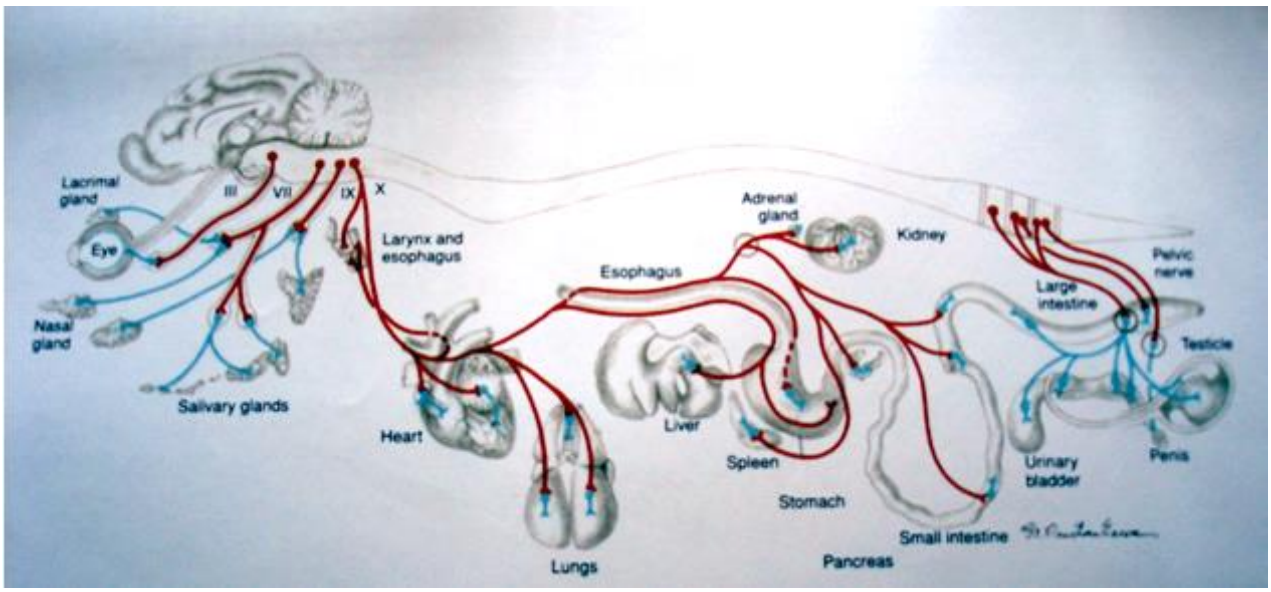
DIFFERENCES BETWEEN SYMPATHETIC AND PARASYMPATHETIC NERVOUS SYSTEM:

Sympathetic Nervous System (Adrenergic Nervous System)	Parasympathetic Nervous System (Cholinergic Nervous System)
(i) It arises as thoraco-lumbar outflow (T_1 to L_3).	(i) It arises as a craniosacral outflow with 3rd (oculomotor), 7th (facial), 9th (glossopharyngeal), 10th (vagus) and 11th (spinal accessory) cranial nerves along with 2nd, 3rd and 4th sacral nerves.
(ii) Ganglia are nearer to the C.N.S. The ratio of pre- and post-ganglionic fibre is generally 1:20 or more. So, the post-ganglionic fibre is longer.	(ii) Ganglia are away from the C.N.S. and on or close to the organs. The ratio is generally 1:1. So, the post-ganglionic fibre is shorter [Exception- In Auerbach's plexus, the ration is 1:8,000].
(iii) Distributed to effector organs throughout the body.	(iii) Distribution is much more limited.
(iv) Neurotransmitters are acetylcholine (in ganglia) and norepinephrine (at neuroeffector junctions).	(iv) Neurotransmitter is acetylcholine in both ganglia and at neuroeffector junctions.
(v) *Function of Sympathetic Nervous System*: As a generalization, it can be said that activation of the sympathetic changes functions in a direction which fits the body for a period of activity and energy expenditure. For example, blood pressure increases, blood flow is diverted from skin and gut to the CNS and muscles, bronchioles dilate and glycogenolysis & lipolysis reveal mobilization of energy reserves.	*(v) Function of Parasympathetic Nervous System*: Conversely, parasympathetic activity modulates body functions towards the needs of a period of inactivity and repair of energy deficits. Vital functions are slowed, energy consumption is reduced and increased digestive function replenishes the stores and evacuates wastes.
(vi) Sympathetic activity increases in stress and emergency.	(vi) Parasympathetic activity predominates during rest.
(vii) Sympathetic nervous system is responsible for providing continuous stimulus to the organs and the parts supplied.	(vii) The parasympathetic nervous system is endowed with the medullary functions.
(viii) If nerve is cut, the animal will survive with some physiological change.	(viii) If taken out, the function is usually normal but due to conservation of energy, animal will not survive long.



Source: Veterinary Pharmacology & Therapeutics by H. Richard Adams, Blackwell Publishing

Fig. : Anatomical representation of motor innervation from the sympathetic nervous system to various body organs and tissues. Preganglionic sympathetic neuron bodies within thoracolumbar of the spinal cord send axons peripherally to synapse with ganglionic neuron bodies comprising the sympathetic ganglionic chains located along each side of the vertebral column. Postganglionic axons exit sympathetic ganglionic chains and pass peripherally to innervate those cells regulated by the sympathetic (thoracolumbar) division of the autonomic nervous system. Preganglionic fibres are red; postganglionic fibres are blue.



Source: Veterinary Pharmacology & Therapeutics by H. Richard Adams, Blackwell Publishing

Fig. : Anatomical representation of motor innervation from the parasympathetic nervous system to various body organs and tissues. Preganglionic parasympathetic neuron bodies within cranial and sacral zones of the central nervous system send axons peripherally to synapse with ganglionic neuron bodies localized within or adjacent to visceral tissues. Postganglionic axons exit parasympathetic ganglia and innervate those cells regulated by the parasympathetic (craniosacral) division of the autonomic nervous system. Roman numerals depict cranial nerves carrying parasympathetic neurons. Preganglionic fibres are red; postganglionic fibres are blue.

Table: Typical responses of effector tissues to sympathetic and parasympathetic nerve impulses:

Effector tissues	*Sympathetic-mediated responses*[1]	*Parasympathetic -mediated responses*[2]
Heart	General excitation	General inhibition
Sinoatrial (SA) node	β_1 – increase heart rate	Decrease heart rate
Atria	β_1 – increase contractile force, conduction velocity	Decrease contractile force
Atrioventricular (AV) node	β_1 – increase automaticity, conduction velocity	Decrease conduction velocity; AV block
His-Purkinje system		…
Ventricles	β_1 – increase automaticity, conduction velocity	Decrease contractile force[4]
	β_1 – increase contractile force, conduction velocity, irritability[3]	
Blood vessels		
Coronary	α_1 – constriction; β_2 – dilation[5]	Dilation[6]; constriction[6]
Cutaneous, mucosal	α_1 – constriction	Dilation[7]
Cerebral	α_1 – constriction; β – dilation	Dilation[7]
Skeletal muscle	α_1 – constriction; β_2 – dilation[8]	Dilation[7]
Splanchnic	α_1 – constriction; β_2 – dilation[9]	Dilation[7]
Renal	α_1 – constriction; β_2 – dilation[9]	Dilation[7]
Genital	α_1 – constriction	Dilation[10]
Veins	α_1 – constriction	
Endothelium	α_2 – dilation	
GI tract	General inhibition	General excitation
Smooth muscle	β_1 – relaxation; α – relaxation[11]	Increase motility and tone
Sphincters	α – contraction	Relaxation
Secretions	Decrease (usually)	Increase
Gall bladder & ducts	Relaxation	Contraction
Bronchioles		
Smooth muscle	β_2 – relaxation	Contraction
Glands	Inhibition (?)	Stimulation
Eye		
Radial muscle, iris	α_1 – contraction (mydriasis)	…
Sphincter muscle, iris	…	Contraction (miosis)
Ciliary muscle	β – relaxation; far vision	Contraction; near vision
Urinary bladder	Urinary retention	Urination
Fundus	β_1 – relaxation	Contraction
Trigone, sphincter	α – contraction	Relaxation
Splenic capsule	α – contraction, β_2 – relaxation	...
Sweat glands	Secretion (cholinergic); [12]β_2 – Secretion (horse)	
Salivary glands	α_1 – scant, viscous secretion	Profuse watery secretion
Piloerector muscles	α – contraction	…
Kidney rennin release	α_2 – decrease; β_1 – increase	…
Uterus[13]	α_1 – contraction, β – relaxation (non-pregnant > pregnant)	Contraction[14]
Genitalia		
Male	α – ejaculation	Erection[15]
Female	…	Erection[15]
Adrenal medulla	Secretion of epinephrine > norepinephrine (cholinergic)	…
Autonomic ganglia	Ganglionic discharge (cholinergic)	Ganglionic discharge[16]
Liver	β_2 – glycogenolysis and gluconeogenesis (α in some species)	…
Pancreas		
Islet cells	α_2 – decrease; β_2 – increase secretion	…
Acini	α – decrease secretion	Increase secretions
Fat cells	β_1 – lipolysis	…
Adrenergic nerve terminals	α_2 – decrease release of norepinephrine β_2 – increase release of norepinephrine	± Release of norepinephrine[17]
Platelets	α_2 – aggregation	…

Note: Superscript numbers are defined as follows:

(1) α and β designate the principal adrenoceptor type subserving a tissue response. α_1, α_2, β_1 and β_2 designate the receptor subtype. The usual receptor types are presented; considerable interspecies variation exists, particularly with reference to subtypes.

(2) Except when otherwise designated (e.g. ganglia), parasympathetic responses are subserved by muscarinic receptors.

(3) Catecholamine-induced irritability of the myocardium may be associated with β_1 and α receptors, systemic pressor response may contribute.

(4) Muscarinic receptors subserving decreased contractility are demonstrable in ventricular muscle, but the significance is not definitely known.

(5) In small coronary arteries, β receptors are more numerous, more sensitive, and/or more responsive than α receptors. In large coronary arteries, α receptors can be demonstrated. β_1 and β_2 subtypes differ depending upon species.

(6) Depending upon experimental conditions, cholinergic effects on coronary blood vessels have been reported as both constriction and dilation.

(7) Arterial smooth muscle generally is not innervated by the parasympathetic nervous system (exceptions include blood vessels in genitalia). Thus cholinergic receptors in most arterial beds are not associated with parasympathetic nerves. In certain regions (e.g arteries of skeletal muscles) sympathetic cholinergic vasodilator fibers are present, but their physiologic importance is poorly understood.

(8) In skeletal muscle arteries β receptors are more sensitive than α receptors.

(9) β receptors of visceral blood vessels seem less important than α receptors.

(10) Parasympathetic-induced dilation of genital blood vessels (which contributes to erection) is not mediated by ACh: the neurotransmitter is believed to be nitric oxide; see (15) below.

(11) β-inhibitory receptors may be localized on smooth muscle cells, whereas α-inhibitory receptors may be localized on parasympathetic cholinergic (excitatory) ganglionic cells of Auerbach's plexus.

(12) In humans, sweat glands are innervated by post ganglionic sympathetic axons that release ACh (i.e., cholinergic) rather than norepinephrine (i.e., adrenergic). In domestic animals, however, sweat glands are regulated by adrenergic (e.g., horse) or cholinergic mechanisms, depending upon species and type of gland.

(13) Uterine responses vary depending on species and stage of estrous, pregnancy and menstrual cycle (when present).

(14) Contractile responses dominate; cholinergic drugs can induce severe myometrial contractions and abortion.

(15) Smooth muscle erectile tissue is relaxed by parasympathetic impulses, thereby leading to vascular space engorgement and erection. The neurotransmitter at these sites is not ACh but it is believed to be nitric oxide.

(16) Ganglionic transmission is subserved predominantly by nicotinic receptors.

(17) In many blood vessels endothelial α_2 receptors mediate vasodilation through the release of endothelial-derived nitric oxide. In contrast, α_2 receptors of vascular smooth muscle subserve vasoconstriction.

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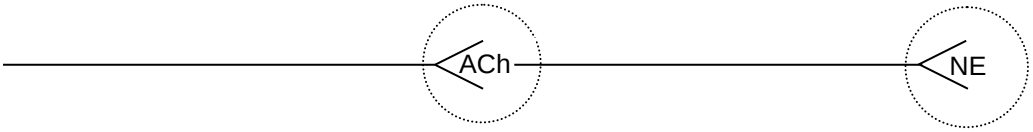
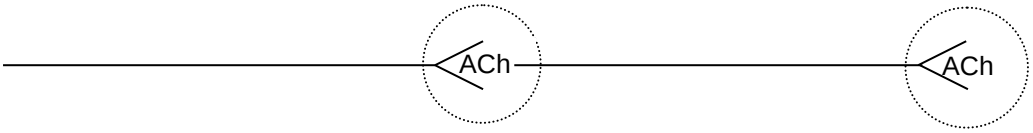
TYPES OF AUTONOMIC FIBRES:

Sympathetic Fibres:

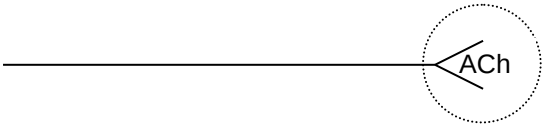
(i) Sympathetic adrenergic:



(ii) Sympathetic cholinergic: Supplies to salivary, bronchial and sweat glands of all animals except sheep and horses.

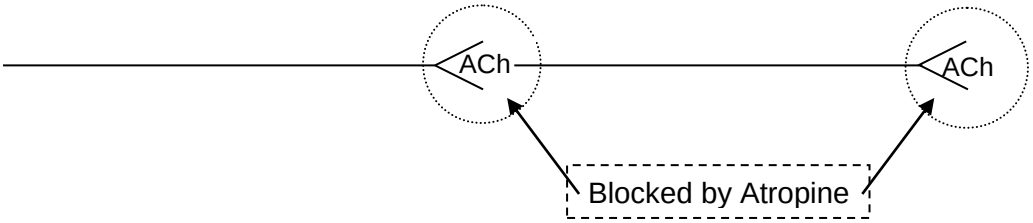


(iii) Sympathetic splanchnic cholinergic or sympathetic preganglionic fibre : Supplies to adrenal gland.

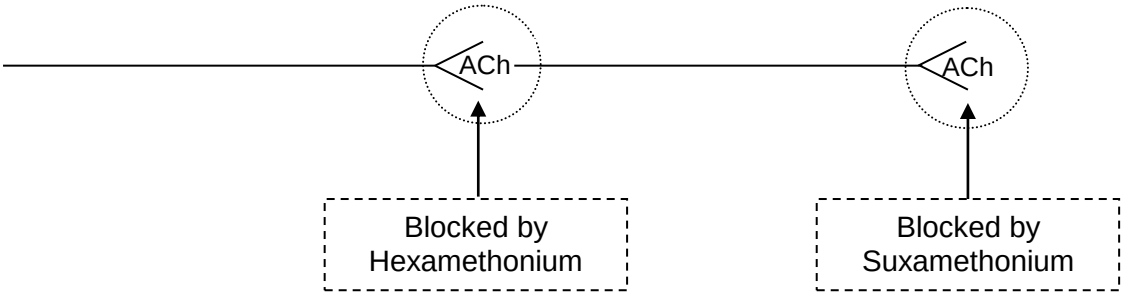


Parasympathetic Fibres:

(i)



(ii)



CENTRAL AUTONOMIC CONNECTIONS:

There is no any exclusive autonomic area in the C.N.S.; considerable intermixing and integration of somatic and autonomic innervation occurs. The highest seat regulating autonomic functions is in hypothalamus – posterior and lateral nuclei are primarily sympathetic while anterior and medial nuclei are primarily parasympathetic. Many autonomic centres (pupillary, vagal, respiratory etc.) are located in the mid-brain and medulla in relation to the cranial nerves. The lateral column in the thoracic spinal cord contains cells which give rise to the sympathetic outflow.

GENERAL FUNCTIONS OF THE AUTONOMIC NERVOUS SYSTEM:

The integrating action of the autonomic nervous system is of vital importance for the well being of the organism. In general, the autonomic nervous system regulates the activities of the structures that are not under voluntary control and that function below the level of consciousness. Thus, respiration, circulation, digestion, body temperature, metabolism, sweating and the secretions of certain endocrine glands are regulated, in part or entirely, by the autonomic nervous system. The constancy of internal environment of the organism is to a large extent controlled by the vegetative or autonomic nervous system.

The sympathetic system and its associated adrenal medulla are not essential to life in a controlled environment. Under circumstances of stress, however, the lack of sympathoadrenal functions becomes evident. Body temperature can not be regulated when environmental temperature varies; the concentration of glucose in blood does not rise in response to urgent need; compensatory vascular response to haemorrhage, oxygen deprivation, excitement and exercise are lacking; resistance to fatigue is lessened; sympathetic components of instinctive reactions to the external environment are lost; and other serious deficiencies in the protective forces of the body are discernible.

The sympathetic system normally is continuously active; the degree of activity varies from moment to moment and from organ to organ. In this manner, adjustments to a constantly changing environment are accomplished. The sympathoadrenal system also can discharge as a unit. This occurs particularly during rage and fright, when sympathetically innervated structures over the entire body are affected simultaneously. Heart rate is accelerated; blood pressure rises; red blood cells are poured into the circulation from the spleen (in certain species); blood flow is shifted from the skin and splanchnic region to the skeletal muscles; blood glucose rises; the bronchioles and pupil dilate, and on the whole, the organism is better prepared for “fight or flight”. Many of these effects result primarily from, or are reinforced by, the actions of epinephrine, secreted by adrenal medulla. In addition, signals are received in higher brain centres to facilitate purposeful responses or to imprint the event in memory.

The parasympathetic system is organized mainly for discrete and localized discharge. Although, it is concerned primarily with conservation of energy and maintenance of organ function during periods of minimal activity, its elimination is not compatible with life. Sectioning the vagus, for example, soon gives rise to pulmonary infection because of the inability of cilia to remove irritant substances from the respiratory tract. The parasympathetic slows the heart rate, lowers the blood pressure, stimulates GI movements and secretions, aids absorption of nutrients, protects the retina from excessive light, and empties the urinary bladder & rectum. Many parasympathetic responses are rapid and reflexive in nature.

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Chapter - 2

Neurohumoral Transmission

NEUROHUMOURAL TRANSMISSION

Neurohumoural transmission implies that nerves transmit their message across synapses and neuroeffector junctions by the release of humoural (chemical) messengers.

HISTORICAL ASPECTS:

1857, Dubois Raymond – Observed similarity between transmission of nerve impulse produced electrically as well as by chemical substances such as NH_3, lactic acid etc.

- 1901, Lewandowsky & Langley – Noted independently the similarity between the effects of injection of extracts of the adrenal gland and stimulation of sympathetic nerves.
- 1910, Berger & Dale – Noted that the effect of sympathetic nerve stimulation were more closely produced by primary sympathomimetic amines, then by secondary sympathomimetic amines.
- 1914, Sir Henry Dale – Thoroughly investigated the pharmacological properties of ACh which produced responses exactly similar to parasympathetic nerve stimulation and he *introduced the term "parasympathomimetic"* to characterize the effects of ACh.
- 1921, Otto Loewi – He provided the first direct evidence for the chemical mediation of nerve impulses by peripheral release of specific chemical agents. He electrically stimulated the vagus nerve of an isolated perfused frog heart.

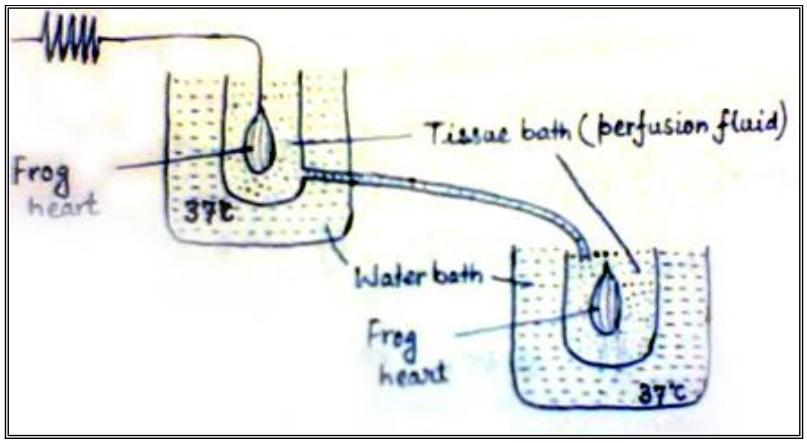


Figure : Showing Otto Loewi Experiment.

The perfusate leaving this preparation was reperfused through another frog heart. Upon stimulation of the vagus nerve to the first heart, Loewi observed that this heart was immediately depressed. Within a few seconds, the second heart was also depressed. Certainly, the most logical explanation for this finding was that stimulation of vagus nerve liberated a chemical "myocardial inhibitory" substance that was carried in the perfusate to the second heart. He referred this substance as Vagusstoff (Vagus substance) or parasympathin which was later recognized as acetylcholine.

- 1946, Von Euler – He showed that the sympathetic transmitter is noradrenaline.

CRITERIA FOR BEING A NEUROHUMOURAL TRANSMITTER:

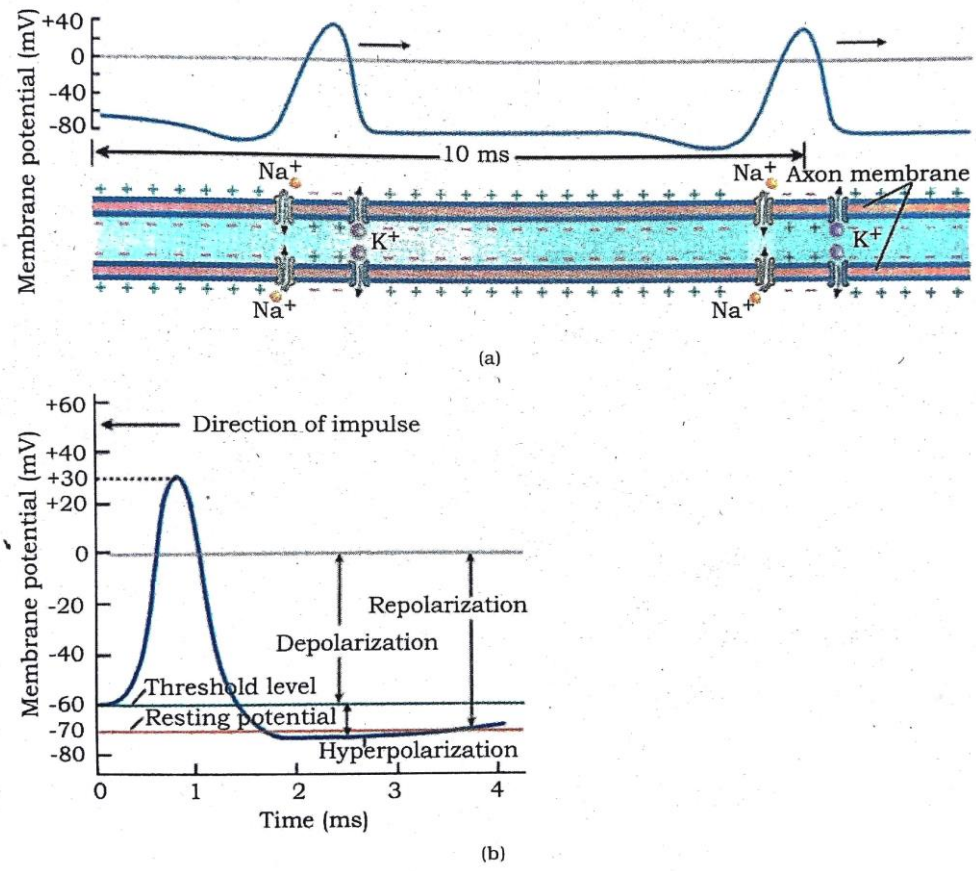
To be considered as a post-junctionally acting neurohumoural transmitter a substance must fulfill the following criteria –

(i) It should be present in the presynaptic neurone (usually along with the enzymes synthesizing it).
(ii) It should be released in the medium following nerve stimulation.
(iii) Its application should produce responses identical to those produced by nerve stimulation.
(iv) Its effects should be antagonized or potentiated by other substances which similarly alter effects of nerve stimulation.

STEPS INVOLVED IN NEUROHUMOURAL TRANSMISSION:

AXONAL CONDUCTION:

Axonal conduction refers to the passage of an impulse along a nerve fibre. It is dependent upon selective changes in the permeability of the axonal membrane to electrolytes. At rest, membrane potential within mammalian axons is approximately -70 mV. This negative intracellular potential is maintained at rest basically because



Source: NCERT Biology

Figure : A typical action potential in an axon. (a) Potential distribution across the axonal membrane, (b) Relationship between membrane potentials.

the axonal membrane is more permeable to K^+ than to Na^+. Na^+ ions are in higher concentration in extracellular than in intracellular fluid, whereas K^+ ions are in greater concentration in intracellular than in extracellular fluid. The relatively small amounts of K^+ that leak in the interstitial space in conjunction with the large number of organic anions that are intracellular result in a net negative charge within the axons.

An action potential reflects a reversal of the polarization state present at rest and is the result of permeability changes that occur at the axonal surface as an impulse is propagated along a nerve fibre. A suprathreshold stimulus initiates a localized change in the permeability of axonal membrane. Suddenly, permeability of the fibre to Na^+ ion is greatly increased in relation to K^+; Na^+ moves inward in the direction of its large electrochemical gradient. The movement is detected by an instantaneous change in the membrane potential in a positive direction. The positively charged Na^+ increases in concentration within the axon; the membrane potential moves from – 70 mV toward zero and then overshoots to the extent that momentarily the inside of the fibre is positive in relation to the exterior of the cell.

Repolarization of the membrane occurs rapidly as the selective permeability characteristics of the axonal membrane are quickly reestablished. The axon once again becomes relatively impermeable to Na^+ and relatively more permeable to K^+, and the negativity of the interior of the cell is quickly reestablished.

Although, not important in axonal conduction, Ca^{2+} channels in other tissues (e.g., heart) contribute to the action potential by prolonging depolarization by an inward movement of Ca^{2+}. This influx of Ca^{2+} also serves as a stimulus to initiate intracellular events.

Although, the localized permeability changes associated with an action potential are extremely short-lived, they elicit similar alterations in membrane function in immediately adjacent quiescent areas of the axon. Thus the axon potential is a self-propagating, and in this manner an action potential is conducted along an axonal fibre.

Axonal conduction is insensitive to most drugs. Even local anaesthetics must be used in high concentrations in immediate contact with a nerve before excitability is blocked.

The axonal conduction is blocked by certain toxins such as **Tetradotoxin** (puffer fish poison) and **Saxitoxin** (shell fish toxin), which interfere with the Na^+ entry across the neuronal membrane during depolarization. **Batrachotoxin**, a steroidal alkaloidal toxin elaborated by a type of South American frogs, paralyses the nerves by persistent depolarization as a result of increase in Na^+ influx. Local anaesthetics act by preventing the Na^+ influx and depolarization of the nerve.

JUNCTIONAL TRANSMISSION:

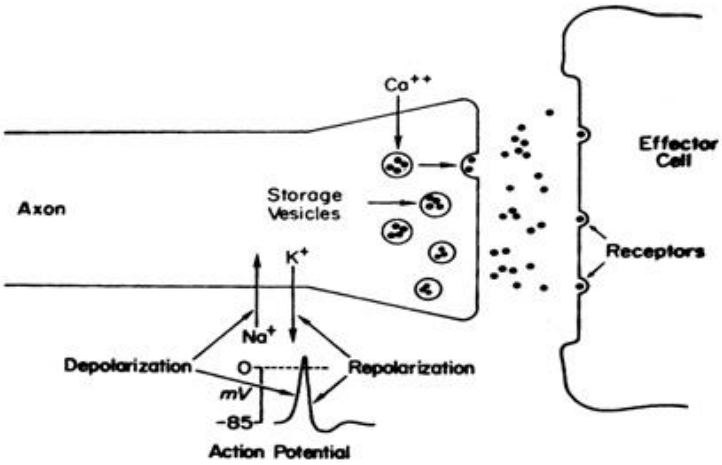
The arrival of the action potential at the axonal terminals initiates a series of events that trigger transmission of an excitatory or inhibitory impulse across the synapse or neuroeffector junction. These events are as follows:

(i) Storage and release of the transmitter:

The non-peptide neurotransmitters are largely synthesized in the region of axonal terminals and stored there in synaptic vesicles. Peptide neurotransmitters are found in large dense-core vesicles which are transported down the axon from their site of synthesis in the cell body.

During the resting state, there is a continual slow release of isolated quanta of the transmitter; this produces electrical responses at the post-junctional membrane (miniature end plate potentials, ***mepps***) that are associated with the maintenance of physiological responsiveness of the effector organ. A low level of spontaneous activity within the motor units of skeletal muscle is particularly important, since skeletal muscle lacks inherent tone.

Release of neurotransmitter substance is triggered by arrival of the axonal action potential at the nerve terminal. The action potential causes the synchronous release of several hundred quanta of neurotransmitter. Depolarization of the axonal terminal triggers this process; a critical step in most but not all nerve endings in the influx of Ca^{2+}, which enters the axonal cytoplasm and promotes fusion between the axoplasmic membrane and those vesicles in close proximity to it. The contents of the vesicles, including enzymes and other proteins, then are discharged to the exterior by a process termed *exocytosis*.



Source: Veterinary Pharmacology & Therapeutics by H. Richard Adams, Blackwell Publishing

Figure : Schematic representation of neurohumoural transmission

The axonal action potential (AP) represents a self-propagating depolarization-repolarization of the axon that is characterized by an influx of Na^+ and an efflux of K^+. As the AP arrives at the nerve terminal, it facilitates an inward movement of Ca^{2+}, which triggers the discharge of neurotransmitter (●) from storage vesicles into the junctional cleft. Neurotransmitter reacts with the specialized receptor areas on the post-junctional membrane and initiates a physiologic response in the effector cell.

(ii) Combination of the transmitter with post-junctional receptors and production of the post-junctional potential:

The released transmitter combines with the specific receptors on the post-junctional membrane and depending upon its nature an Excitatory Post Synaptic Potential (*EPSP*) or an Inhibitory Post Synaptic Potential (*IPSP*) is produced.

EPSP **-** Increase in permeability to all cations causes Na^+ or Ca^{2+} influx (through fast or slow channels) which cause depolarization followed by K^+ efflux (repolarization). These ionic movements are passive as the flow is down the concentration gradients. Electrically these changes are characterized as Excitatory Post Synaptic Potential, which then propagates localized permeability changes in adjacent portions of the cell membrane and an action potential is conducted along the remainder of the innervated cell.

IPSP - Increase in permeability to smaller ions, i.e. K^+ and Cl^- (hydrated K^+ ion is smaller than hydrated Na^+ ion) only, so that K^+ moves out and Cl^- moves in (in the direction of their concentration gradients). Thus, it causes an increase in the net negative charge within the cell and actually hyperpolarizes the post synaptic membrane. The resulting hyperpolarization of the membrane increases the threshold to stimuli and, in effect, elicits an inhibitory response in the cell.

(iii) Initiation of post-junctional activity:

If an EPSP exceeds a certain threshold value, it initiates a propagated action potential in the post-synaptic neurone or a muscle action potential in skeletal or cardiac muscle. In smooth muscles, an EPSP may increase the rate of spontaneous depolarization, effect the release of Ca^{2+} and enhance muscle tone; in gland cells, the EPSP initiates secretion through Ca^{2+} mobilization. An IPSP, which is found in neurons and smooth muscles but not in skeletal muscles, will tend to oppose excitatory potentials simultaneously initiated by other neuronal sources.

(iv) Destruction or dissipation of the transmitter:

Following its combination with the receptor, the transmitter is either locally degraded (e.g. ACh) or is taken back into the pre-junctional neurone by active uptake or diffuses away (e.g. NE, GABA). Rate of termination of transmitter action governs the rate at which responses can be transmitted across a junction (1 to 1000/ second).

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Chapter - 3

Cholinergic Neurotransmission

CHOLINERGIC NEUROTRANSMISSION

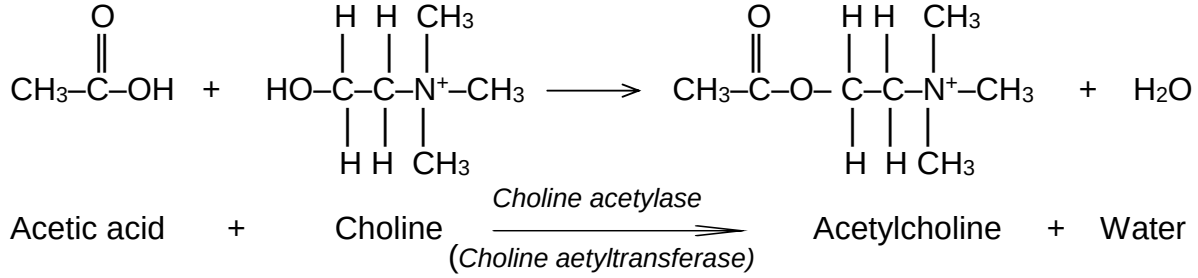
CHOLINERGIC TRANSMISSION:

The impulse transmission on nerve or neuroeffector junction that is mediated by acetylcholine (ACh) is called cholinergic transmission. The different sites of cholinergic transmission are –

1. Parasympathetic neuroeffector junctions
2. Autonomic ganglia
3. Adrenal medulla
4. Somatic myoneural junctions
5. Certain regions of CNS.

SYNTHESIS, STORAGE, RELEASE AND CATABOLISM OF ACETYLCHOLINE:

Synthesis:



Acetylcholine is synthesized within cholinergic nerves by the enzymatic transfer of an acetyl group from acetyl CoA to choline. This reaction is catalyzed by the enzyme *choline acetylase* (also referred to as *choline acetyltransferase*). This acetyl CoA may also come from pyruvate metabolism. Choline is taken into the neurone from the plasma and the above enzymatic reactions occur within the neurone.

Hemicholinium (a synthesis blocker of ACh) competitively blocks choline uptake in the neurone and thus depletes the ACh stores in the neurone terminals. Uptake of choline is the rate limiting step in the biosynthesis of ACh.

Storage:

After synthesis in the cytoplasm, ACh is transferred to axonal vesicles in the nerve terminals where it is stored for release whenever necessary. Transport of ACh into synaptic vesicles is blocked by **Vesamicol** (storage blocker).

Release:

When an action potential comes to the synapse or nerve terminal, then Ca^{2+} channel is opened and Ca^{2+} enters the synaptic membrane from outside and fuses with the vesicles to cause exocytosis and release of ACh. Two toxins interfere with cholinergic transmission by affecting release – **Botulinum toxin** (release blocker) inhibits release, while **Black widow spider toxin** induces massive release and depletion.

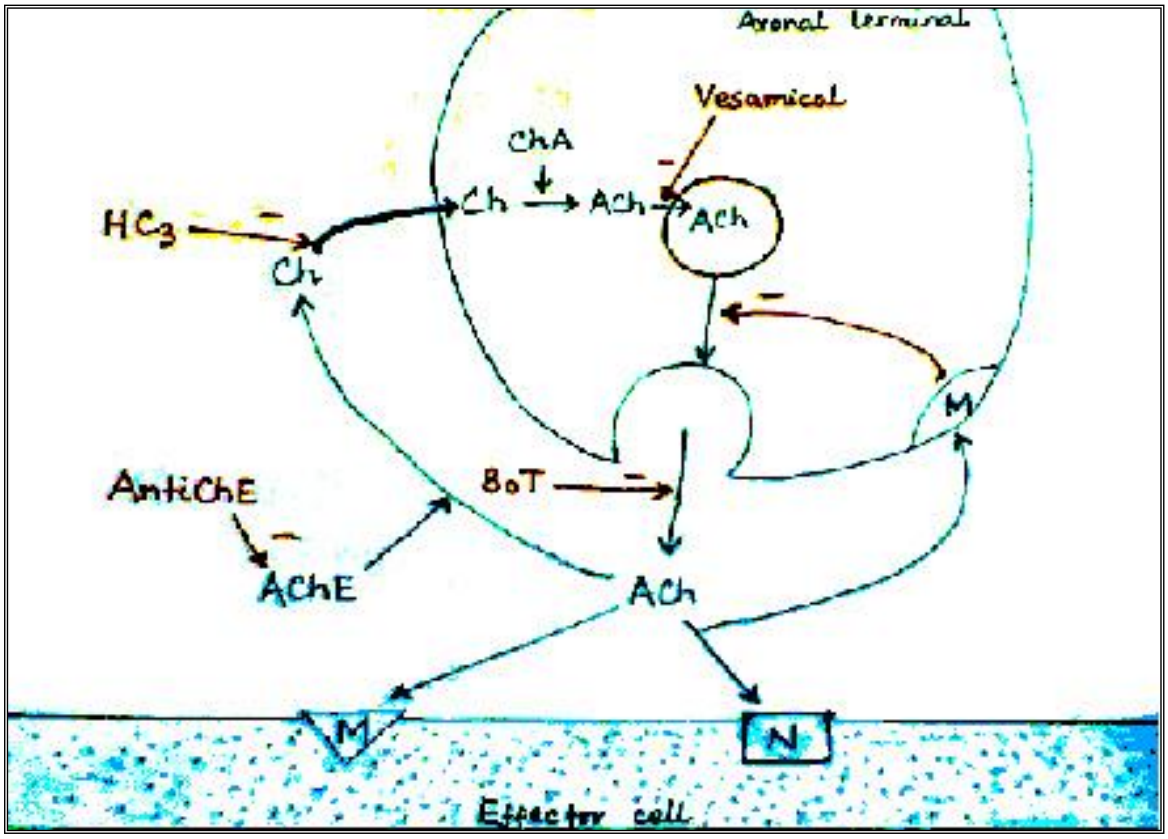


Figure : Showing cholinergic neuronal mechanisms

[(Minus sign showing inhibition), M = Muscarinic receptor, N = Nicotinic receptor, Ch = Choline, ChA = Choline acetylase, HC_3 = Hemicholinium, BoT = Botulinum toxin]

Destruction of ACh:

After serving the transmitter function, ACh within the junctional space is rapidly inactivated by hydrolysis by a specific enzyme, acetylcholine esterase (AChE). AChE is present in cholinergic nerves, autonomic ganglia and neuromuscular & neuroeffector junctions.

$$\text{Acetylcholine} + H_2O \xrightarrow{\textit{Acetylcholinesterase (AChE)}} \text{Acetic acid} + \text{Choline}$$

A somewhat similar enzyme, butyrylcholinesterase (a pseudocholinesterase) is present in serum and other body tissues. It is primarily synthesized in the liver and its likely vestigial physiological function is the hydrolysis of ingested esters from plant sources.

Differences between two types of cholinesterases:

	Acetylcholinesterase (True Cholinesterase)	Butyrylcholinesterase (Pseudo-cholinesterase)
(i) Distribution	All cholinergic sites, RBCs, gray matter.	Plasma, liver, intestine, white matter
(ii) Hydrolysis		
ACh	Very fast (in microseconds)	Slow
Methacholine	Slower than ACh	Not hydrolyzed
Benzoylcholine	Not hydrolyzed	Hydrolyzed
Butyrylcholine	Not hydrolyzed	Hydrolyzed
(iii) Inhibition	More sensitive to Physostigmine	More sensitive to organophosphates
(iv) Function	Termination of ACh action	Hydrolysis of ingested esters.

CHOLINERGIC RECEPTORS:

There are two basic types of cholinergic receptors i.e. Muscarinic receptors (G-protein coupled receptors) and Nicotinic receptors (Ligand gated cation channels).

Small doses of nicotine mimicked certain actions of ACh and large doses inhibited the same ACh responses. The nicotinic responsive sites were found to be present in autonomic ganglia, adrenal medullary chromaffin cells and also the neuromuscular junction of somatic nervous system. Accordingly, receptors on these sites were called as Nicotinic cholinergic receptors.

A mushroom plant (*Amanita muscaria*) alkaloid, muscarine was found to mimic the activity of ACh at the parasympathetic neuroeffector junctions in heart muscle, smooth muscle and secretory glands but not at the previously described nicotinic receptors. So, the type of receptors present at cholinergic neuroeffector junctions in muscle and glands were designated as Muscarinic cholinergic receptors.

Muscarinic receptors:

These are selectively stimulated by muscarine and blocked by atropine, and are located primarily on autonomic effector cells in heart, blood vessels, eye, smooth muscles and glands of gastrointestinal, respiratory and urinary tracts, sweat glands etc. and in the CNS.

Subtypes of Muscarinic receptors:

Muscarinic receptors have been divided into 5 subtypes i.e. M_1, M_2, M_3, M_4 and M_5. Out of these, the first three have been functionally characterized while responses mediated by through M_4 and M_5 subtypes are not well defined. Most organs have more than one subtype, but usually one subtype predominates in a given tissue.

Table: Characteristics of important subtypes of Muscarinic receptors

	M_1	**M_2**	**M_3**
Location and function subserved	Autonomic ganglia: Depolarization Gastric glands: Histamine release and acid secretion CNS: Not precisely known	SA node: Hyperpolarization, lowered rate of impulse generation AV node: Lowered velocity of conduction Atrium: Shortening of action potential duration, decreased contractility. Ventricle: Lowered contractility (slight) - due to sparse cholinergic receptors Cholinergic nerve endings: Decreased ACh release	Visceral smooth muscles: Contraction Exocrine glands: Secretion Vascular endothelium: Release of nitric oxide (NO) → vasodilatation
Agonist	Oxotremorine	Methacholine	Bethanechol
Antagonist	Pirenzepine, Telenzepine	Methoctramine	Hexahydrosiladifenidol

M_1 receptors: Primarily a ***neuronal receptor*** located on ganglionic cells and central neurons especially in cortex, hippocampus and corpus striatum. It plays a major role in mediating gastric secretion and relaxation of lower oesophageal sphincter on vagal stimulation.

M_2 receptors: **Cardiac** Muscarinic receptors are predominantly M_2 and mediate vagal bradycardia.

M_3 receptors: **Visceral smooth muscle** contraction and **glandular** secretions are elicited through M_3 receptors which also mediate **vasodilatation** through EDRF (Endothelial derived relaxing factor) release. Together M_2 and M_3 receptors mediate most of the well recognized Muscarinic actions including contraction of lower oesophageal sphincter.

Nicotinic receptors:

These receptors are selectively stimulated or activated by nicotine and blocked by tubocurarine or hexamethonium. On the basis of location and selective agonists and antagonists, two types of nicotinic receptors i.e. N_M and N_N (previously called N_1 and N_2) have been recognized.

N_M or N_1 receptors (Nicotinic muscular): These are present at skeletal muscle end plates: are selectively stimulated by phenyl trimethylammonium (PTMA) and blocked by tubocurarine. They mediate skeletal muscle contraction.

N_N or N_2 receptors (Nicotinic neuronal): These are present on ganglionic cells (sympathetic as well as parasympathetic), adrenal medullary cells & in spinal cord and certain areas of brain. They are selectively stimulated by dimethylphenyl piperazinium (DMPP) and blocked by hexamethonium and constitute the primary pathway of transmission in ganglia.

Table: Characteristics of subtypes of Nicotinic receptors

	N_M or N_1	**N_N or N_2**
Location and function subserved	Neuromuscular junction: Depolarization of muscle end plate → contraction of skeletal muscle.	Autonomic ganglia: Depolarization → post-ganglionic impulse. Adrenal medulla: Catecholamine release. CNS: Site specific excitation or inhibition.
Agonists	PTMA, Nicotine	DMPP, Nicotine
Antagonists	Tubocurarine, α-Bungarotoxin	Hexamethonium, Trimethaphan

ACTIONS OF ACETYLCHOLINE:

Muscarinic actions:

(1) Heart: SA node – Hyperpolarization, Rate of impulse generation reduced and bradycardia.

AV node & His-Purkinje fibres – Conduction slowed.

Atria – The force of atrial contraction is markedly reduced.

Ventricles – Contractility also reduced but not marked.

(2) Blood vessels: All blood vessels are dilated. Thus, there is fall in B.P. Muscarinic receptors are present on vascular endothelial cells: vasodilatation is primarily mediated through the release of an endothelial dependent relaxing factor (EDRF) which is nitric oxide (NO). It may be due to inhibitory action of ACh on NA release from tonically active vasoconstrictor nerve endings.

(3) Smooth muscles: Smooth muscles in most organs are contracted. Tone and peristalsis in the GI tract is increased and sphincters relax → abdominal cramps and evacuation of bowel.

Peristalsis in ureter is increased. The detrusor muscle contracts while the bladder trigone and sphincters relax → voiding of urine.

Bronchial muscles constrict, asthmatics are highly sensitive → dyspnoea, precipitation of an attack of bronchial asthma.

(4) Glands: Secretion from all parasympathetically innervated glands is increased → sweating, salivation, lachrimation, tracheobronchial and gastric secretion. The effect on pancreatic and intestinal glands is not marked. Secretion of milk and bile is not affected.

(5) Eyes: Contraction of circular muscles of iris → miosis

Contraction of ciliary muscles of iris → spasm of accommodation, increased outflow facility, reduction in intraocular tension (especially in glaucomatous patients).

Nicotinic actions:

(1) Autonomic ganglia: Both sympathetic and parasympathetic ganglia are stimulated. The effect is manifested at higher doses. High dose of ACh given after atropine causes tachycardia and rise in B.P.

(2) Skeletal muscles: Contraction of fibre, fasciculations etc.

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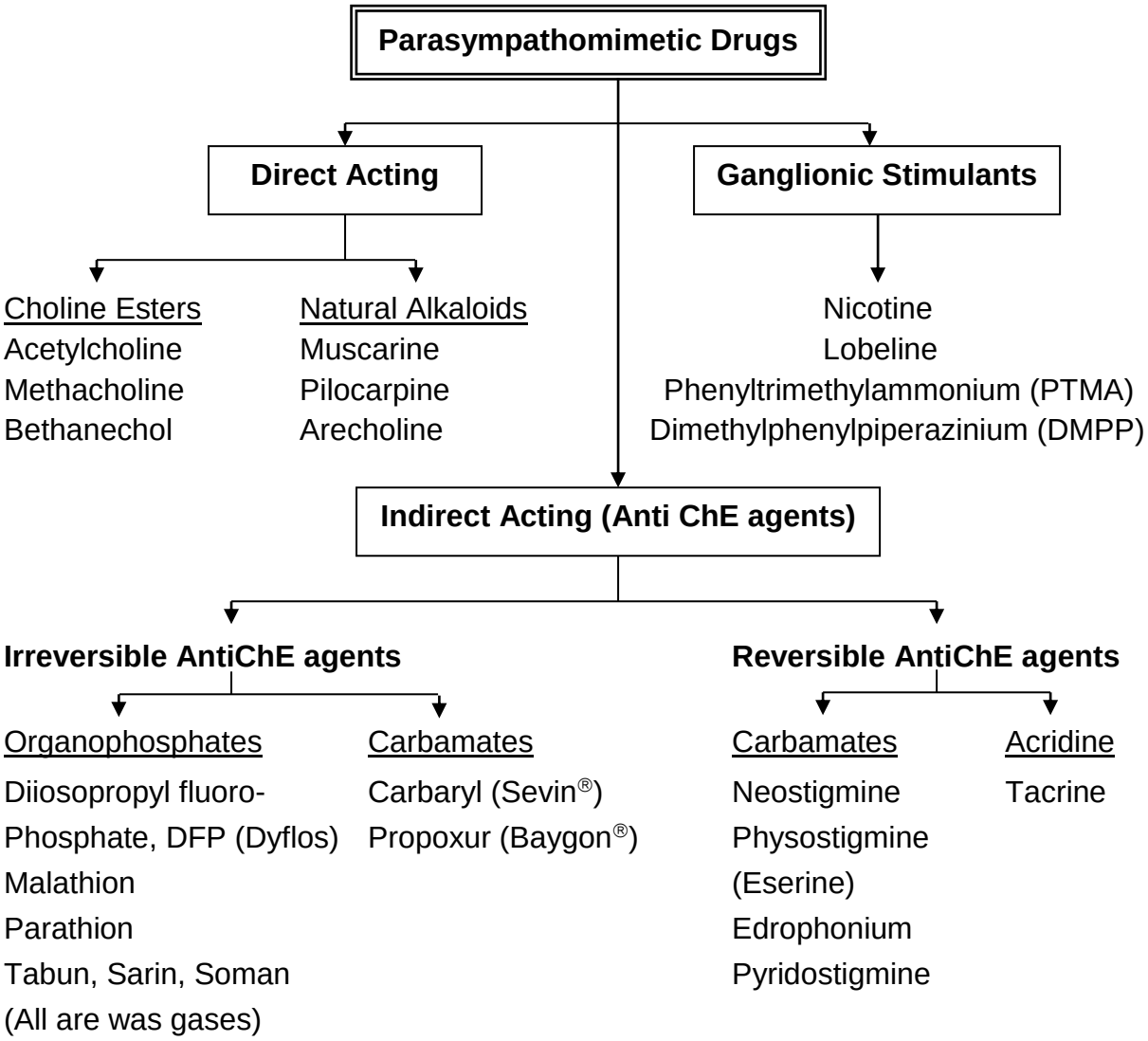
Chapter - 4

Cholinergic Drugs (Parasympathomimetics)

CHOLINERGIC DRUGS (Parasympathomimetics)

These are the drugs which mimic the effects of parasympathetic post-ganglionic nerves or those of acetylcholine. These are also called as cholinergics, cholinergic agonists or cholinomimetics. These drugs also have agonistic action on cholinergic receptors at autonomic ganglia, neuromuscular junction etc.

CLASSIFICATION:



(I) CHOLINE ESTERS:

(1) Acetylcholine (ACh): Although is essential for maintenance of body homeostasis, it is not used therapeutically for two important reasons:

(i) It acts simultaneously at various tissue sites and no selective therapeutic response can be achieved.

(ii) Its duration of action is quite brief because it is rapidly inactivated by the cholinesterases.

(2) Methacholine (Acetyl-β-methylcholine): It is a synthetic choline ester used occasionally in human therapeutics but infrequently (rarely) employed in veterinary medicine.

Methacholine causes muscarinic effects on cardiovascular function similar to those produced by ACh, but it is considerably less active on GI system. Methacholine lacks nicotinic action.

Methacholine is a cholinomimetic of choice for controlling tachycardias of atrial origin. It will cause slowing of heart, reduction of the force of contraction & generalized vasodilatation. *Main site of action of methacholine is the pacemaker*.

(3) Carbachol (Carbamoylcholine): It is an extremely potent choline ester that is active at both muscarinic and nicotinic receptors and therefore caused pharmacological effects similar to changes evoked by ACh. These are particularly prominent on the nicotinic receptors of autonomic ganglia; however, this drug is also very potent at muscarinic sites. For instance, *intravenous injection of doses as small as 2μg/kg causes a transient slowing of heart rate and hypotension* owing to muscarinic effects.

Carbachol is sometimes used for the emergency treatment of colic in the horse and ruminal stasis in cattle. Administration of carbachol is done with great care and the drug is given in repeated small doses of 1-2 mg subcutaneously.

(4) Bethanechol (Carbamoylmethylcholine): It is somewhat similar to methacholine and carbachol, however it is primarily a muscarinic agonist, and has little stimulant effects on nicotinic receptors.

Table: Showing properties of choline esters

Choline esters	Hydrolyzed by		Actions		Selective actions on
	AChE	BuChE	Muscarinic	Nicotinic	
ACh	++	+	+	+	Non-selective
Methacholine	+	–	+	±	CVS
Carbachol	–	–	+	+	GIT, Bladder
Bethanechol	–	–	+	–	GIT, Bladder

Therapeutic uses of choline esters:

(i) Methacholine and bethanechol are not used frequently in clinical veterinary medicine. Methacholine has been used in human medicine to control tachycardia of supraventricular origin.

(ii) Bethanechol, 1 mg administered subcutaneously *b.i.d.* has been used to treat *urinary bladder atony in cats* after incidence of urolithiasis.

(iii) Carbachol has been used in the treatment of colic and impactions of the intestinal tract. It is also used in the treatment of ruminal atony and impaction in cattle.

However, none of the above have proved satisfactory results, so, now-a-days, these are not used clinically on routine basis.

(II) NATURAL ALKALOIDS:

(1) Pilocarpine: It is obtained from the leaves of Brazilian shrubs *Pilocarpus jaborandi* and *P. microphyllus*. It has prominent muscarinic actions and also stimulates ganglia – mainly through ganglionic muscarinic receptors. Pilocarpine is particularly effective in stimulating flow of secretions from exocrine glands, including salivary, mucous, gastric and digestive pancreatic secretions. As with acetylcholine, it causes contraction of GI smooth muscle, thereby increasing smooth muscle tone and peristaltic activity. Of considerable importance, Pilocarpine has a potent constrictor effect on the pupil. Applied to the eye, it penetrates cornea and promptly causes miosis, ciliary muscle contraction and fall in intraocular tension lasting 4-8 hours.

(2) Arecholine: It is an alkaloid found in the beetle nut, the seed of the beetle palm (*Areca catechu*). It has muscarinic as well as nicotinic actions including those on skeletal muscle end plate. It is similar to Pilocarpine in scope of activity but is considerably more potent. It stimulates secretion of the glands of the digestive tract and increases peristaltic movement of the gut. Increased flow of the saliva occurring within 5 minutes following a subcutaneous injection and lasting for an hour is particularly noticeable. Arecholine contracts the urinary bladder.

(3) Muscarine: It is found in the poisonous mushrooms *Amanita muscaria*, and has only muscarinic actions. It is not used therapeutically, but, is of toxicological importance.

Therapeutic uses of cholinomimetic alkaloids:

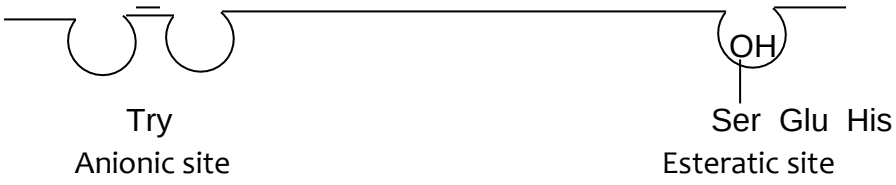
(i) Clinically, solutions of 0.5 to 2% of pilocarpine are used for instillation into the conjunctival sac for treatment of glaucoma.

(ii) Other uses of pilocarpine as a miotic are – to counteract mydriatics after they have been used for testing refraction and to prevent or break adhesions of iris with lens or cornea by alternating it with mydriatics.

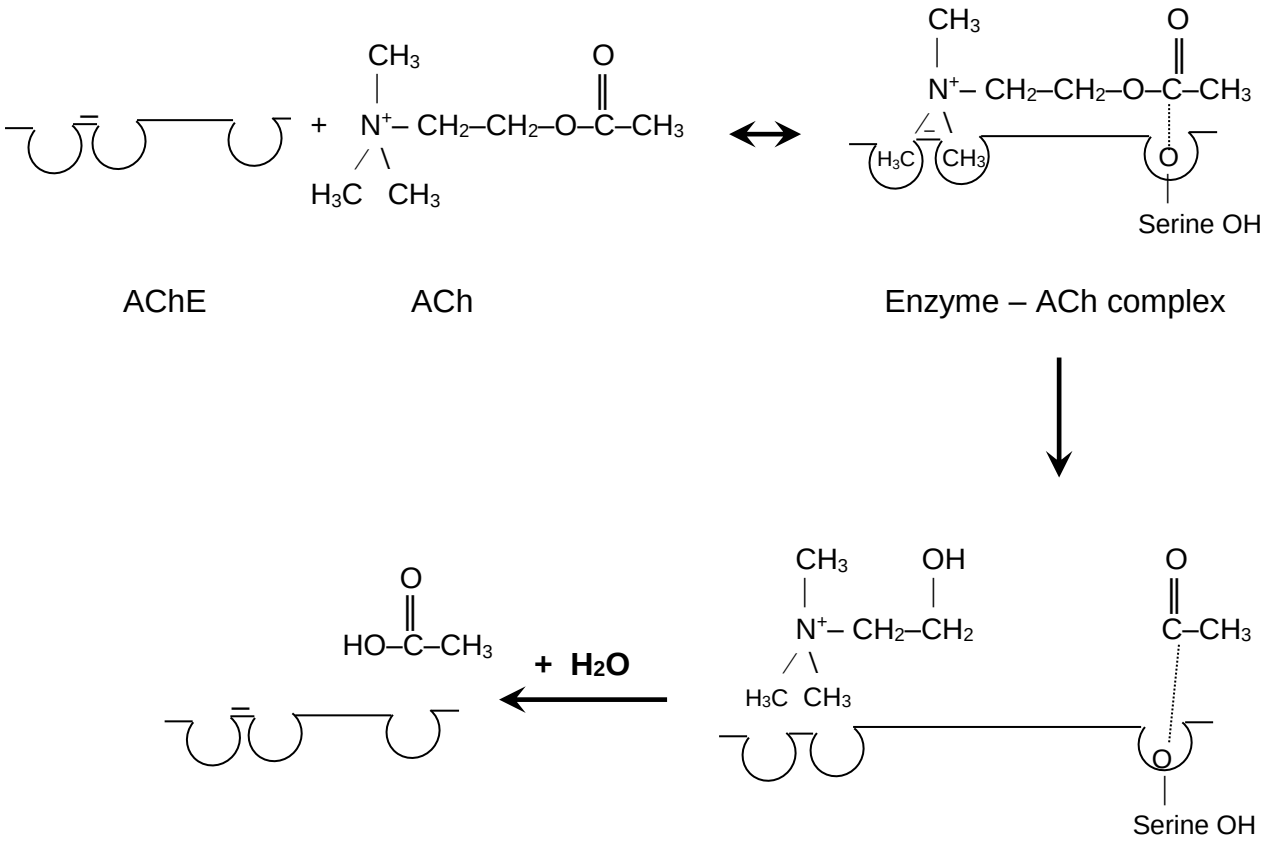
(III) CHOLINESTERASE INHIBITORS:

These are indirect acting parasympathomimetic agents. They inactivate or inhibit AChE and pseudoChE and thereby intensify the activity of endogenous ACh.

Acetylcholinesterase: The active region of AChE forms a gorge which contains an aromatic anionic site formed by tryptophan and an esteratic site formed by serine, glutamate and histidine.



Hydrolysis of ACh by AChE: Hydrolysis of ACh involves electrostatic attraction of positively charged N^+ of ACh to the aromatic pocket and nucleophilic attack by serine –OH which is activated by the adjacent histidine leading to acetylation of the serine. The acetylated enzyme reacts with water to produce acetic acid and choline. The reaction is very fast.



REVERSIBLE INHIBITORS:

Mechanism of action: These agents reversibly bind to the active sites of the enzyme, as they serve as alternate substrates for AChE. Edrophonium and tacrine attach only to the anionic site of the enzyme and tacrine inhibited enzyme does not involve hydrolysis of the inhibitor, but only its diffusion – so action is brief, whereas physostigmine and neostigmine bind to both anionic and esteratic sites of the enzyme. So, the carbamylation of the enzyme (with neostigmine and physostigmine) is of longer duration than the inhibition by edrophonium.

Thus, during the period where the enzyme inhibitor complex exists, the enzyme will not hydrolyze its natural substrate ACh.

(1) Physostigmine: It is an alkaloid extracted from the dried ripe seeds of a vine, *Physostigma venenosum* which grows in tropical West Africa. It is also known as Calabar bean or "Ordeal bean". Now-a-days, physostigmine is used for its ability to constrict the pupil or as miotic and in the **treatment of deadly nightshade poisoning**.

(2) Neostigmine: It is the salt of a synthetically produced substance structurally related to physostigmine. It is used as purgative and in the treatment of atony of urinary bladder.

Table showing comparative features of Physostigmine and Neostigmine

	Physostigmine	**Neostigmine**
1. Source	Calabar bean	Synthetic
2. Chemistry	Tertiary amine derivative	Quaternary ammonium compound
3. Oral absorption	Good	Poor
4. CNS actions	Present	Absent
5. Applied to eye	Penetrates cornea	Poor penetration
6. Direct action on cholinoceptors	Absent	Present
7. Prominent effect on	Autonomic effectors	Skeletal muscle
8. Important use	Miotic (in glaucoma)	Myasthenia gravis
9. Dose	0.5 – 1 mg (man) oral or parenteral 0.1 – 1% in eye drops.	0.5 – 2.5 mg (man) i.m./ s.c
10. Duration of action	Systemic - 4 to 6 hours Eye – 6 to 24 hours	4 to 6 hours.

IRREVERSIBLE INHIBITORS:

Mechanism of action: Organophosphates act as irreversible inhibitors of the cholinesterases in mammals. These compounds irreversibly phosphorylate the esteratic site of both AChE and the non-specific or the pseudocholinesterase throughout the body. Endogenous ACh is not inactivated and the resulting effects are due to the excessive preservation and accumulation of endogenous ACh.

Effects and toxicity: Organophosphate poisoning produces diffuse cholinomimetic effects: profuse salivation, vomiting, defaecation, hypermotility of the GI tract, urination, bradycardia, hypotension, severe bronchoconstriction and excess bronchial secretions. These signs reflect excess activation of muscarinic receptors of post-ganglionic parasympathomimetic actions.

In addition to the muscarinic effects, skeletal muscle fasciculations, twitching and subsequently muscle paralysis occur. These effects are due to persistent excessive stimulation of the nicotinic receptors of skeletal neuromuscular junctions, resulting in the depolarizing type of striated muscle paralysis. Convulsions and frequently death are seen in organophosphate poisoning caused by the penetration of the agents into the CNS and subsequent intensification of the activity of ACh at CNS sites.

Treatment of organophosphate poisoning:

1. The first line of treatment consists of administration of atropine to counter muscarinic effects of ACh @ 0.2 to 0.5 mg/kg b.wt. (maximum dose = 1 mg/kg). It is administered as 0.15% solution of atropine in physiological saline.
2. The second line of treatment involves the use of oxime reactivators such as diacetyl monoxime (DAM), 2-pyridine aldoxime methiodide (2-PAM or pralidoxime), obidoxime etc. which reactivate the phosphorylated AChE enzyme and greatly accelerates clinical recovery. It also serves to reduce the quantity of atropine required.

The usefulness of oxime reactivators is limited to a short period (minutes or hours depending on the compound) because the enzyme phosphate complex becomes resistant when a further group is removed by hydrolysis, a change known as "ageing".

Therapeutic use of Irreversible inhibitors:

(i) The only drug indication is the relief of glaucoma where a single instillation of dyflos (di-isopropylfluorophosphate) or echothiopate acts for several weeks.

(ii) Organophosphates and carbamates are used as insecticides for the control of insect vectors and ectoparasites.

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Chapter - 5

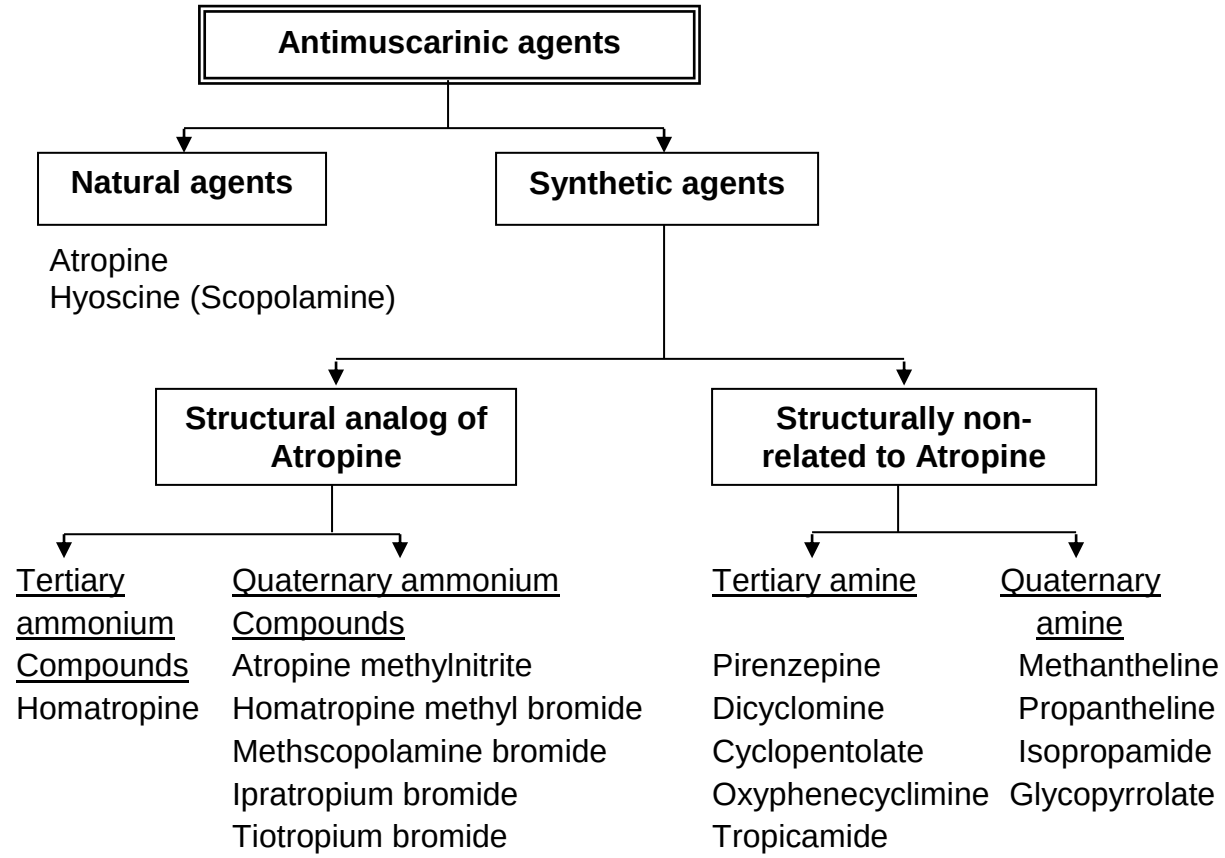
Anticholinergic Drugs (Parasympatholytics)

ANTICHOLINERGIC DRUGS (Parasympatholytics)

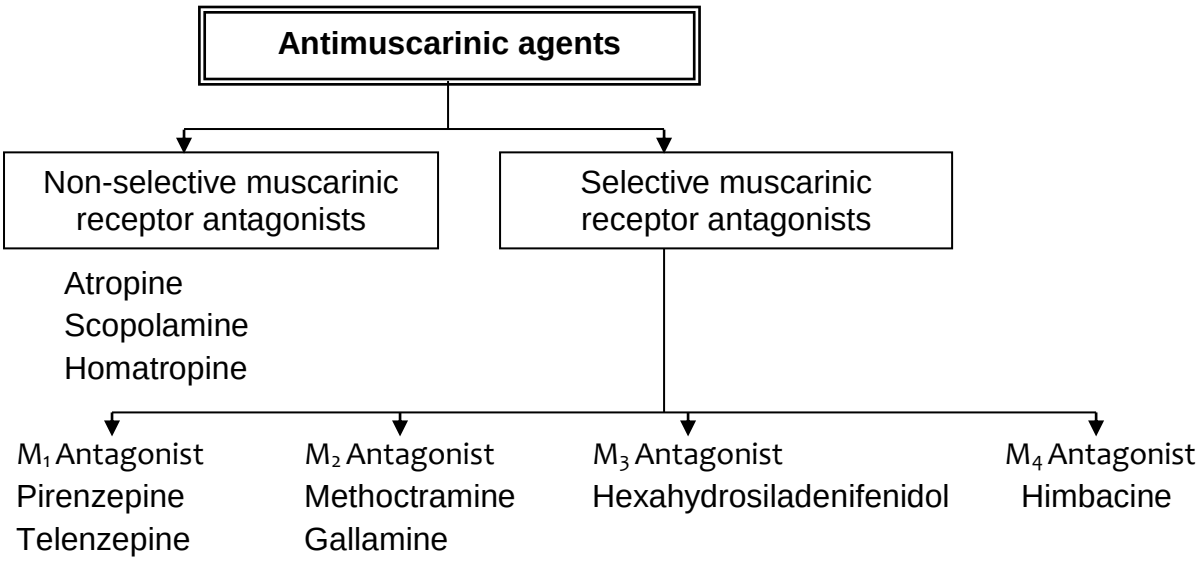
These drugs block muscarinic receptors only, so better known as antimuscarinic agents.

CLASSIFICATION:

(I) Classification based on Origin & Structure:



(II) Classification based on Mode of Action:



Mechanism of action of muscarinic blockers:

Atropine and related drugs block the cholinergic muscarinic receptors by acting as competitive antagonists of ACh or other direct acting cholinergic drugs.

PHARMACOLOGICAL ACTIONS OF PARASYMPATHOLYTICS:

(1) Cardiovascular system: Small doses of atropine cause an initial temporary bradycardia (agonistic action due to vagal stimulation and/ or momentary stimulation of cardiac muscarinic receptors prior to their blockade). High doses cause tachycardia. Atropine like drugs antagonize the fall in blood pressure caused by choline esters. Atropine alone does not affect blood pressure.

(2) GI tract: Smasmolytic effect on GI smooth muscles by preventing the effect of endogenous ACh. Block the increase in tone and motility of GIT caused by cholinergic drugs. Rumen motility is reduced. GI secretions including salivation are blocked.

(3) Respiratory tract: Inhibition of bronchial secretions and dilatation of bronchi (temporary relief of dyspnoea/ asthma/ heaves in horses).

(4) Eye: Mydriasis and cycloplegia (paralysis of accommodation) following local or systemic use. Mydriasis is due to blockade of cholinergic influence and dominance of adrenergic effect. Cycloplegia is due to paralysis of ciliary muscle of the lens.

(5) Urinary tract: Spasmolytic effect on ureters (useful in the treatment of renal colic) and urinary retention (relaxation of bladder).

(6) Skin: Anhydrotic action in man (cholinergic) and consequently rise in body temperature but does not prevent sweating in horses (adrenergic).

(7) CNS: Atropine has no significant effect. Scopolamine in small doses produces depression & excitement and delirium at high doses in cats and dogs.

ATROPINE & SCOPOLAMINE:

☞ Atropine is an alkaloid extracted from the leaves of belladonna plants *Atropa belladonna* (deadly nightshade), *Datura stramonium* (Jimson weed) and *Hyoscyamus niger* (Henbane). Scopolamine is also an alkaloid extracted from the leaves *Hyoscyamus niger* and *Scopolia carniolica*.

☞ **The name "*Atropa belladonna*":** During the time of the Roman Empire and in the Middle Ages, the deadly nightshade shrub was frequently used to produce an obscure and often prolonged poisoning, prompting Linnaeus to name the shrub *Atropa belladonna*, after Atropos, the oldest of the three Fates (goddesses) in Greek mythology, who cuts the thread of life. The name *belladonna* derives from the alleged use of this preparation by Italian women to dilate their pupils; modern-day fashion models are known to use this same device for visual appeal.

☞ Atropine is a racemic mixture of d-hyoscyamine and l-hyoscyamine. The laevo form of hyoscyamine is biologically active.

☞ In atropine poisoning, physostigmine is used as it is better able to enter CNS than other parasympathomimetics. It is the central effects of atropine which is lethal.

☞ Rabbits possess an esterase (atropinase) which hydrolyses atropine and is thereby able to feed on deadly nightshade with freedom without showing any toxic symptom.

☞ The laevo isomer of hyoscine is called scopolamine which is the active form. Its main difference from atropine is its slight sedative effect on the CNS at therapeutic dosage.

☞ **Effects of atropine in relation to dose:**

Dose	Effects
0.5 mg/kg	Slight cardiac slowing; some dryness of mouth; inhibition of sweating.
1 mg/kg	Definite dryness of mouth; thirst; acceleration of heart, sometimes preceded by slowing; mild dilation of pupils.
2 mg/kg	Rapid heart rate; palpitation; marked dryness of mouth; dilated pupils; some blurring of near vision.
5 mg/kg	All the above symptoms marked. Difficulty in speaking and swallowing; restlessness and fatigue; headache; dry, hot skin; difficulty in micturition; reduced intestinal peristalsis.
10 mg/kg or more	Above symptoms more marked, pulse rapid & weak; iris practically obliterated; vision very blurred; skin flushed, hot dry & scarlet; ataxia; restlessness, excitement, hallucinations and delirium; coma and finally death.

THERAPEUTIC USES OF PARASYMPATHOLYTICS:

(i) Atropine:
- As preanaesthetic
- As antidote in organophosphate and carbamate poisoning (0.2 to 0.5 mg/kg : 1/4th of the total dose should be given i.v. and rest by i.m. route).
- For relief of heaves in horses.
- Eye drops (1%) – during eye examination.

(ii) Homatropine: 2 – 5 % solution topically in the eye for ophtalmological use (mydriatic or cycloplegic). Its effects are of shorter duration as compared to those of atropine which causes persistent mydriasis and cycloplegia.

(iii) Glycopyrrolate: Preanaesthetic.

[NB: Alternate use of a mydriatic (e.g. atropine) and a miotic (e.g. physostigmine 0.5%) can be used to prevent adhesions involving the iris.**]**

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Chapter - 6

Adrenergic Neurotransmission

ADRENERGIC NEUROTRANSMISSION

ADRENERGIC TRANSMISSION:

The impulse transmission that is mediated by norepinephrine (post-ganglionic sympathetic nerve terminals and CNS), dopamine (CNS) and epinephrine (adrenal medulla) is in general called as adrenergic transmission. All these transmitters are also called as catecholamines.

CATECHOLAMINES:

Norepinephrine, epinephrine and dopamine are endogenous catecholamines; they are sympathetic neural and humoural transmitter substances in most mammalian species.

Norepinephrine: It acts as transmitter at most peripheral sympathetic neuroeffector junctions and in the CNS.

Epinephrine : It is the major hormone released from adrenal medulla.

Dopamine : It is believed to transmit impulse information in specific areas within the CNS (basal ganglia, limbic system, CTZ, anterior pituitary etc.).

SYNTHESIS OF CATECHOLAMINES:

Norepinephrine is synthesized from the amino acid phenylalanine in a stepwise process summarized below:

(i) The aromatic ring of phenylalanine is hydroxylated by action of an enzyme, phenylalanine hydroxylase. The reaction yields tyrosine.

(ii) Tyrosine is converted to dihydroxyphenylalanine (DOPA) by the enzyme tyrosine hydroxylase. This reaction involves additional hydroxylation of the benzene ring, and it is believed to represent the rate limiting step in catecholamine synthesis.

(iii) DOPA is decarboxylated by the enzyme L-amino acid decarboxylase (dopa decarboxylase) to dihydrophenylethylamine (dopamine). Dopamine is then taken up in the storage granule.

Conversion of tyrosine to DOPA to dopamine is believed to occur within the axonal cytoplasm (axoplasm). In some central anatomic sites (e.g. mammalian extrapyramidal system), dopamine seems to act as the primary neurotransmitter rather than its metabolites norepinephrine and epinephrine.

(iv) In peripheral adrenergic neurons and adrenal medullary chromaffin cells, intragranular dopamine is hydroxylated in the β-position of the aliphatic side chain by dopamine-β-hydroxylase to form norepinephrine.

(v) In the adrenal medulla, norepinephrine is released from the granules of chromaffin cells and is N-methylated within the cytoplasm by phenylethanolamine N-methyltransferase to form epinephrine. Epinephrine is subsequently localized in another type of intragranular storage granule prior to its release from the adrenal medulla.

[**NB:** Adrenal medulla contains 80-90% of epinephrine and rest norepinephrine].

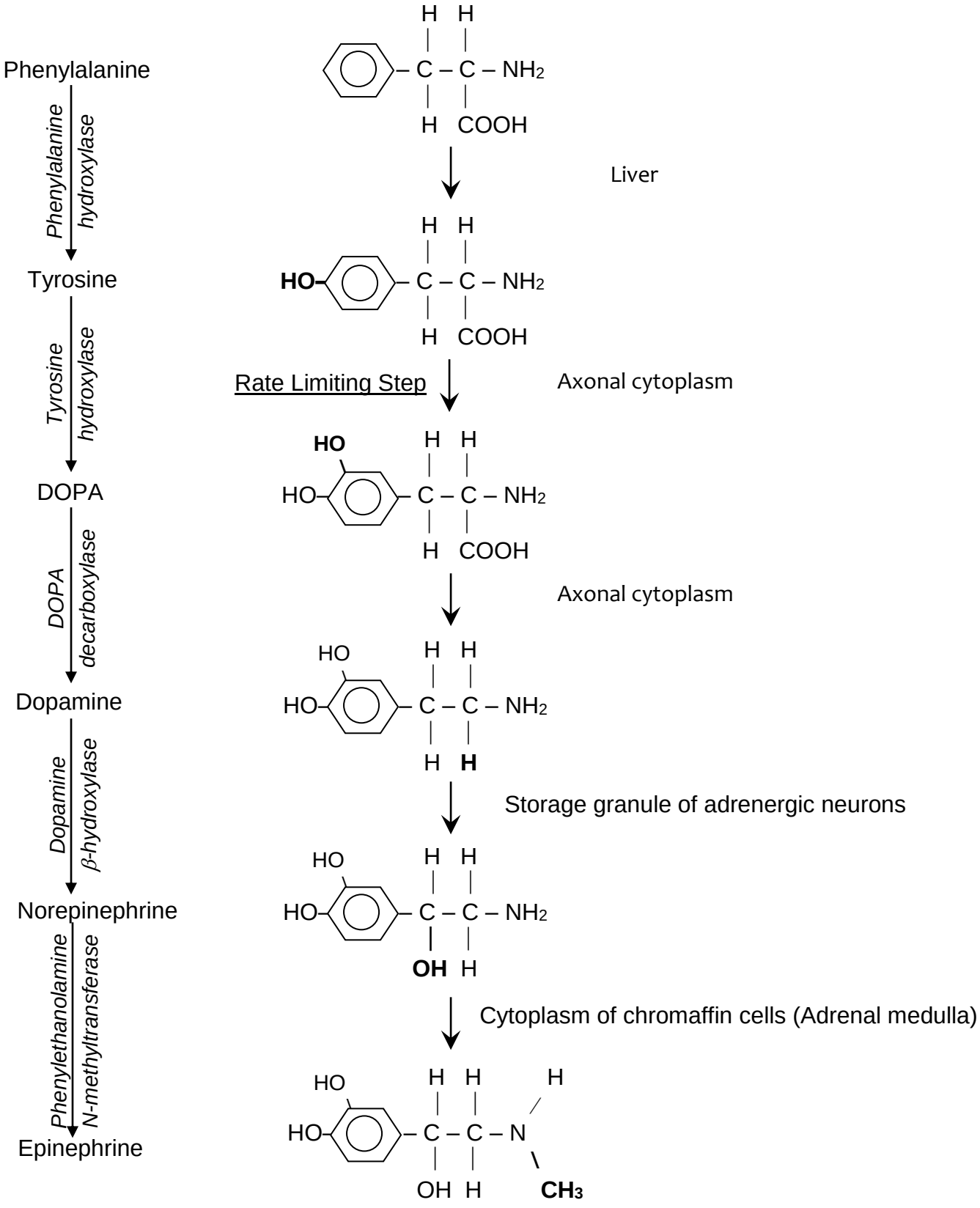

Figure: Steps involved in the synthesis of catecholamines

STORAGE OF CATECHOLAMINES:

Catecholamines are taken up from the cytoplasm into vesicles or granules by an active transport system which is ATP and Mg^{2+} dependent. Storage within the granular vesicles is accomplished by complexation of the catecholamines with ATP (in molecular ratio of 4:1) which is adsorbed on a protein, chromogranin. This complexation renders the amine inactive until their release. The intragranular pool of NE is the principal source of neurotransmitter released upon nerve stimulation. The cytoplasmic pool of catecholamines is kept low by the enzyme monoamine oxidase (MAO) present in neuronal mitochondria.

[**NB:** Reserpine is a drug which depletes catecholamine stores by inhibiting monoamine transport into vesicles].

RELEASE OF CATECHOLAMINES:

The nerve impulse coupled release of catecholamines from adrenergic nerve terminals takes place by exocytosis and is dependent upon an inward movement of Ca^{2+}. Released norepinephrine migrates across the synaptic cleft and interacts with specific adrenergic receptor sites on the post-junctional membrane.

[**NB:** Bretylium inhibits norepinephrine release].

TERMINATION OF CATECHOLAMINES ACTION:

Uptake of Catecholamines:

There is a very efficient mechanism by which norepinephrine released from the nerve terminal is recaptured. Exogenously administered norepinephrine and epinephrine are taken up into sympathetic nerve endings by this uptake process. Conservation of catecholamine neurotransmitters by reuptake is one of the first examples of recycling used products. There are following two uptake mechanisms:

Axonal uptake (Uptake - 1)	Extraneuronal uptake (Uptake -2)
(i) The adrenergic neuronal uptake is referred to as uptake-1. This uptake is the most important mechanism for terminating the action post-junctional action of NE.	(i) It signifies the extraneuronal uptake of catecholamines into surrounding tissue.
(ii) Uptake-1 is saturable and operates at very low physiological concentrations of transmitter.	(ii) Uptake-2 has very large capacity and accumulation operates most effectively at high concentrations of NE.
(iii) Uptake-1 requires Na^+ ions, K^+ ions and ATP and is blocked by cocaine, desipramine & its congeners guanethidine and many H_1 antihistaminics.	(iii) Uptake-2 is less selective, and is not blocked by cocaine but is sensitive to cortisol. It is not of pharmacological importance.

Metabolism of Catecholamines:

The duration of action of catecholamines can be terminated either by reuptake mechanisms or metabolism by enzymes monoamine oxidase (MAO) and catechol o-methyl transferase (COMT).

Cytoplasmic NE is attacked by MAO. The extraneuronal NE which diffuses into circulation is destroyed by COMT in liver and other tissues like kidney, brain etc.

However, metabolism does not play an important role in terminating the action of endogenous catecholamines.

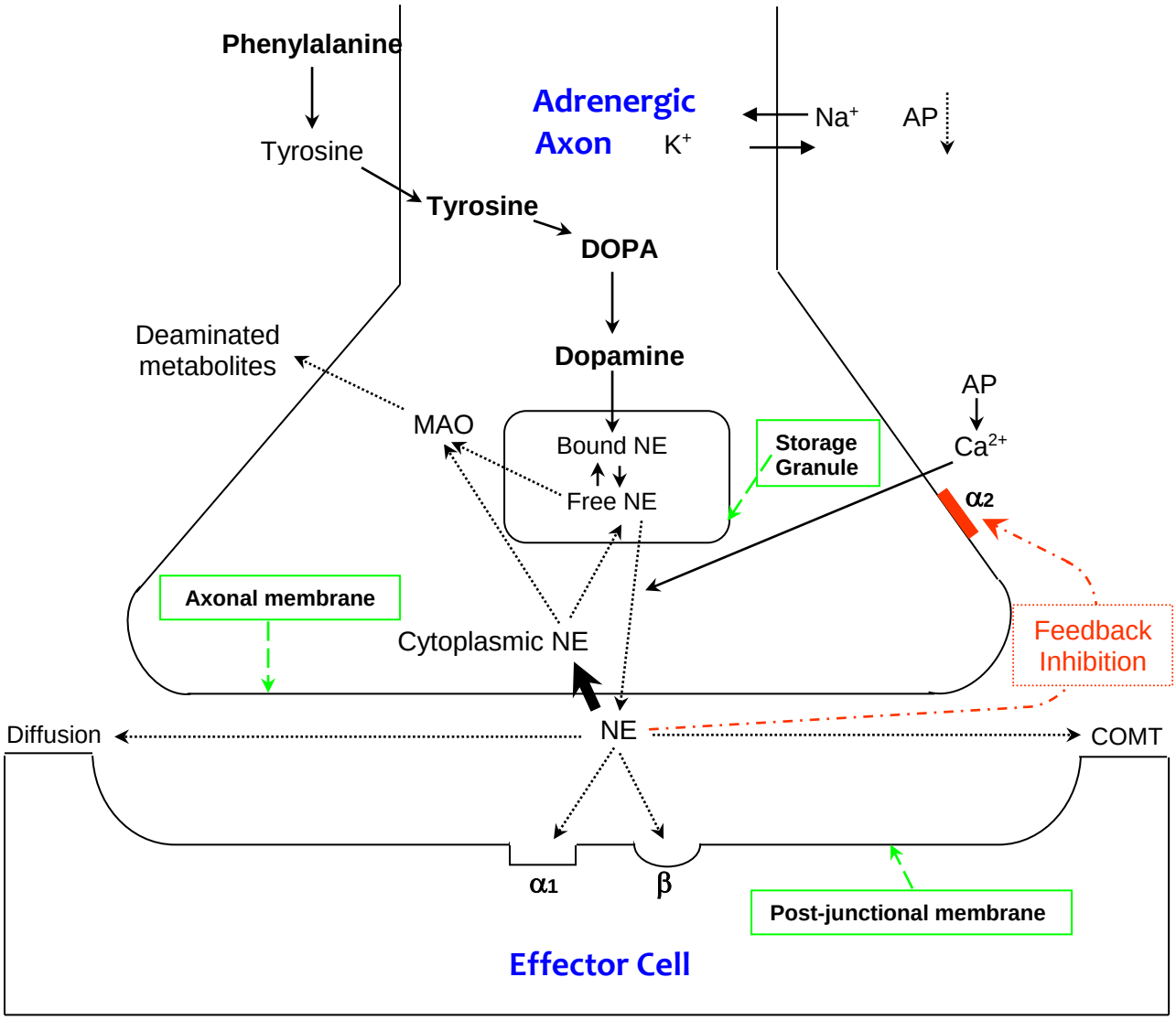

Fig.: Showing neurohumoural transmission at the adrenergic neuroeffector junction

ADRENERGIC RECEPTORS:

Adrenergic receptors have been classified into two types based on rank order of potencies of adrenergic agonists – α and β receptors.

Catecholamines produce excitatory (except GIT) and inhibitory (except CVS) responses on smooth muscles upon activation of α and β receptors, respectively.

α receptors have been further classified into two subtypes – α_1 and α_2. Molecular cloning have further identified three subtypes of α_1 (α_{1A}, α_{1B} & α_{1D}) and three subtypes of α_2 (α_{2A}, α_{2B} & α_{2C}) receptors.

β receptors can be classified in three subtypes – β_1, β_2 and β_3 based on relative organ specificity of selective agonists and antagonists.

Characteristics of subtypes of adrenergic receptors:

Receptor	Agonist	Antagonist	Tissue distribution & Responses
α_1	Epi≥NE>>Iso Phenylephrine	Prazosin	• Vascular smooth muscle - Contraction • Genitourinary smooth m.- Contraction • Liver- Glycogenolysis, gluconeogenesis • Intestinal smooth m. – Relaxation***** • Heart – Increased contractile force
α_2	Epi≥NE>>Iso Clonidine	Yohimbine	• Pancreatic islets- ↓ insulin secretion • Platelets – Aggregation • Nerve terminals – Decreased release of NE • Vascular smooth muscle – Contraction
β_1	Iso> Epi=NE Dobutamine	Metoprolol Atenolol	• Heart – ↑ force & rate of contraction & AV nodal conduction velocity. • Juxtaglomerular cells- ↑ renin secretion
β_2	Iso>Epi>>NE Terbutaline Salbutamol	α-methylpropranolol	• Smooth muscles – Relaxation [vascular, bronchial, GI & genitourinary] • Skeletal muscles – Glycogenolysis. • Liver – Glycogenolysis, gluconeogenesis.
β_3	Iso=NE>Epi	-	• Adipose tissue – Lipolysis.

• EPI ≥ NE >> isoproterenol for α adrenergic receptors.
• Isoproterenol > EPI ≥ NE for β adrenergic receptors.

IMPORTANT:

- **Epinephrine:** α_1 + α_2 + β_1 + β_2 and weak β_3 action.
- **Norepinephrine:** α_1 + α_2 + β_1 + β_3 but no β_2 action.
- **Isoproterenol:** β_1 + β_2 + β_3 but no α action.

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Chapter - 7

Adrenergic Drugs (Sympathomimetics)

ADRENERGIC DRUGS (Sympathomimetics)

These are drugs which mimic the effects of sympathetic stimulation or those of catecholamines. Their effects are due to stimulation of adrenergic receptors (directly or indirectly) on the effector cells, hence also called as adrenergic drugs.

CLASSIFICATION:

(I) Classification based on chemical structure:

(1) Catecholamines: Epinephrine, Norepinephrine, Dopamine and Isoproterenol.

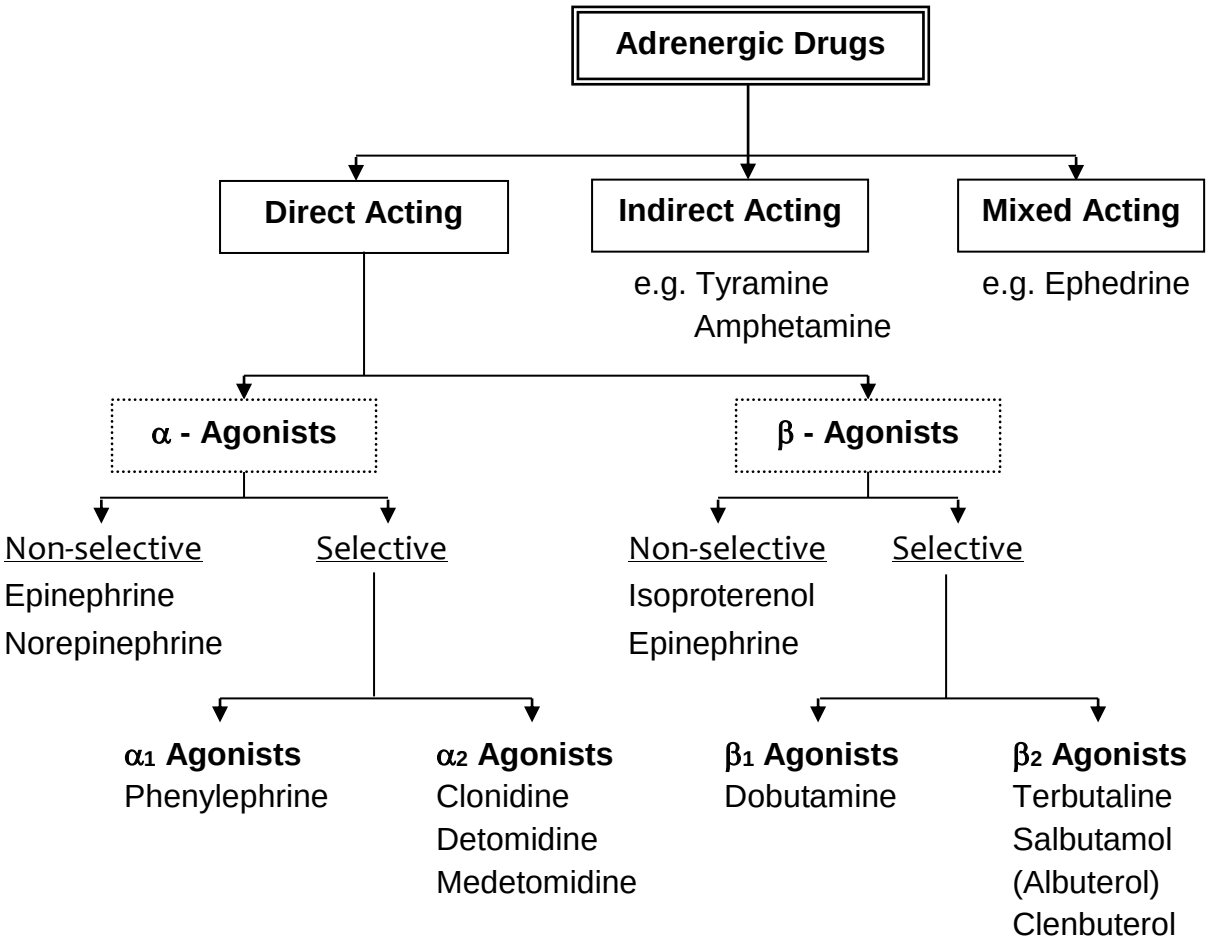
(2) Non-catecholamines: Phenylephrine, Ephedrine, Amphetamine, Tyramine etc.

(II) Classification based on mechanism of action:

(1) Directly acting agents: They act directly as agonists on α and/ or β-adrenergic receptors. e.g. Epinephrine, NE, Isoproterenol.

(2) Indirectly acting agents: They act on adrenergic neurons to release noradrenaline which then acts on the adrenergic receptors. e.g. Tyramine.

(3) Mixed acting agents: They act directly as well as indirectly. e.g. Ephedrine.



PHARMACOLOGICAL EFFECTS OF ADRENERGIC DRUGS:

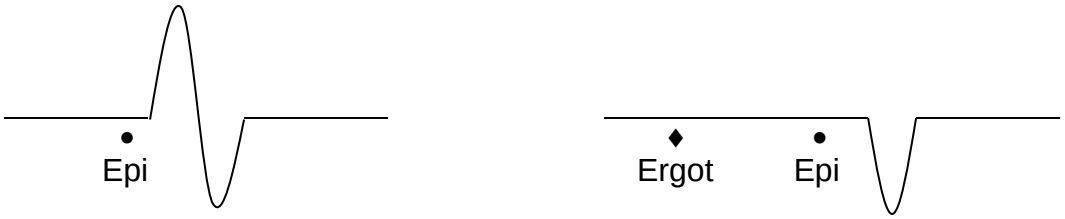
(1) Heart (α_1 & β_1): Increase in heart rate (positive chronotropic effect) and increase in force of cardiac contraction (positive inotropic effect).

(2) Blood vessels (Mainly α_1 but also β_2): Both vasoconstriction (α_1 mediated) and vasodilatation (β_2 mediated) can occur depending on the drug, its dose and vascular bed. There is dilatation of blood vessels in skeletal muscles, lungs and mesentery (β_2 action).

Dale's Reversal Phenomenon or Epinephrine reversal:

Blood vessels contain both α and β_2 receptors. α receptors are more abundant whereas β_2 receptors are less but more powerful and sensitive. Epinephrine causes increase which is followed by decrease in blood pressure. The rise in blood pressure is mediated by α receptors which are more in number. Though β_2 receptors are also occupied by epinephrine, their effect is suppressed by activation of large number of α receptors. As the concentration of epinephrine decreases by metabolism or elimination, it dissociates first from the less sensitive α receptors. So, at later stage, the number of activated β_2 receptors remains more than the activated α receptors which cause decrease in blood pressure.

Now, the presence of α receptor blockers like ergot etc. renders α receptors inactive and inhibits the rising phase of epinephrine induced blood pressure. But, β_2 receptor mediated action (i.e. fall in blood pressure) predominates even at higher concentration of epinephrine as their suppressors (α receptors) are blocked. As the effect of epinephrine is reversed by the presence of α receptor blockers and this phenomenon was first observed by Dale, the phenomenon is called as Dale's Reversal Phenomenon.



(3) Respiratory tract (β_2): Inhibitory effect on smooth muscles of respiratory passages causing relaxation of bronchi and trachea. Epinephrine and isoproterenol (but not norepinephrine) are potent bronchodilators.

(4) Gastrointestinal tract (Both α_1 & β_2): Inhibitory effect on smooth muscles of GI tract causing decrease in tone and motility.

(5) Eye (α_1): Mydriasis due to contraction of radial muscles. Decrease Intraocular Pressure by enhancing both conventional (*via* a β_2-receptor mechanism) and uveoscleral outflow (perhaps *via* prostaglandin production) from the eye.

(6) Sex organ (α_1): Ejaculation of male sex organ.

(7) Metabolism: Metabolic effects like hyperglycaemia (α_1 & β_2) due to glycogenolysis and hyperlipaemia (β_3) due to lipolysis.

(8) Splenic capsule: Contracts (α) and more RBCs are poured into circulation.

(9) CNS: CNS stimulation causing respiratory stimulation, wakefulness, increase in psychomotor activity and anorectic effect.

SYMPATHOMIMETIC AGENTS AND THEIR CLINICAL USES:

(1) Adrenaline (Epinephrine) and Noradrenaline (Norepinephrine): Classically these agents have been used to reverse hypotension, hence, the group name 'pressoramines'.

Noradrenaline – is best used by continuous i.v. infusion (8 μg/ml, 2 ml/min). It causes generalized vasoconstriction with increased peripheral resistance and increased systolic and diastolic blood pressure.

Adrenaline – Myocardial stimulation induced by adrenaline is often accompanied by disordered rhythm of the heart, esp. under trichloroethylene, chloroform, cyclopropane or halothane anaesthesia. For this reason, adrenaline is not given intravenously. Subcutaneously injected adrenaline is still used to relieve the severe hypotension and bronchoconstriction of acute hypersensitivity reactions.

Uses:

(i) With local anaesthetics: Epinephrine and norepinephrine potentiate local anaesthetic action by decreasing absorption of local anaesthetics.

(ii) As local haemostatic: By applying epinephrine moistened gauge or sponge (1 lakh to 1.2 lakh dilutions) over the bleeding surfaces, mucosae or subcutaneous tissues, arrests bleeding due to local vasoconstriction.

(iii) In allergic/ anaphylactic reactions and acute bronchial asthma: Epinephrine reverses the acute hypotension and dilates the respiratory passages.
Cattle & Horses – 4 to 8 ml of 1:1000 dilution i.m. or s.c.
Sheep & Swine – 1 to 3 ml of 1:1000 dilution i.m. or s.c.
Dog & Cat – 1 to 5 ml of 1:10,000 dilution i.m. or s.c.

(iv) As cardiac stimulant: Used in the treatment of acute cardiac arrest AV blocks.

(2) Ephedrine: It is a naturally acting alkaloid obtained from *Ephedra vulgaris.*

- Mixed acting - Mainly acts indirectly but also has some direct action on α & β receptors also.
- It is resistant to MAO and COMT.
- It is 100 times less potent than adrenaline but longer lasting (4 - 6 hour).
- It was the first agent to be used clinically in management of asthma.
- The drug was previously used as bronchodilator, vasoconstrictor, a heart stimulant, a mydriatic and a CNS stimulant. Now-a-days, for most of these purposes, there are preferred drugs which are pharmacologically cleaner, more potent alternatives.

(3) Amphetamine {CNS stimulant}**:** It is a synthetic, orally active, largely indirect acting α & β agonist having euphoriant & habit forming properties in man. It has been used by athletes and given to race horses to improve performance illegally (Doping). The central effects of amphetamine include alertness, increased concentration & attention span, euphoria, talkativeness and increased work capacity. Fatigue is allayed. Hence, athletic performance is improved temporarily followed by deterioration.

(4) Phenylephrine {vasoconstrictor}**:** It is an α_1 agonist (less potent but more long lasting than noradrenaline). It is used in hypotension, in local anaesthetic formulations, in decongestants and in ophthalmology (as 10% solution when pupillary dilatation without loss of accommodation is required).

(5) Isoprenaline (Isoproterenol) {bronchodilator & cardiostimulant}**:** It is a synthetic, mixed β agonist. The drug is resistant to MAO but metabolized by COMT.

- Bronchodilator (β_2) action to asthma in man.
- Powerful cardiostimulatory action (β_1) to accelerate ventricular rate in heart block.

(6) Salbutamol (Albuterol) {bronchodilator}**:** It is a selective β_2 agonist (i.e. acting on bronchial muscle, vasculature and the uterus). β_2 selectivity is only relative. Salbutamol has β_2:β_1 action ratio of 10.

- The drug is lacking the undesirable cardio-excitation side effects of isoprenaline in asthmatics.
- The drug is resistant to MAO and COMT and is having longer duration of action as compared to isoprenaline.
- It is used as **inhaler** by asthmatics. Inhaled salbutamol produces bronchodilatation within 5 minutes and the action lasts for 2 – 4 hours.

(7) Terbutaline {bronchodilator}**:** It is similar to salbutamol in properties and use. Inhaled salbutamol and terbutaline are currently the most popular drugs.

(8) Isoxuprine {tocolytic or uterine relaxant}**:** Selective β_2 agonist. Depresses smooth muscle contraction in gravid uterus. So, useful in threatened abortion.

(9) Clenbuterol: Selective β_2 agonist. It is having tocolytic and bronchodilator actions.

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Chapter - 8

Antiadrenergic Drugs (Sympatholtyics)

ANTIADRENERGIC DRUGS (Sympatholytics)

These are the drugs which antagonize the pharmacological action of sympathomimetic agents or alter the function of sympathetic nervous system inside the body.

CLASSIFICATION:

Antiadrenergic drugs can be classified under two heads:-

(1) Direct acting adrenergic receptor blockers or adrenergic antagonists: These drugs interact with adrenergic receptors and by occupying these sites do not allow an adrenergic agonist access to the receptor.

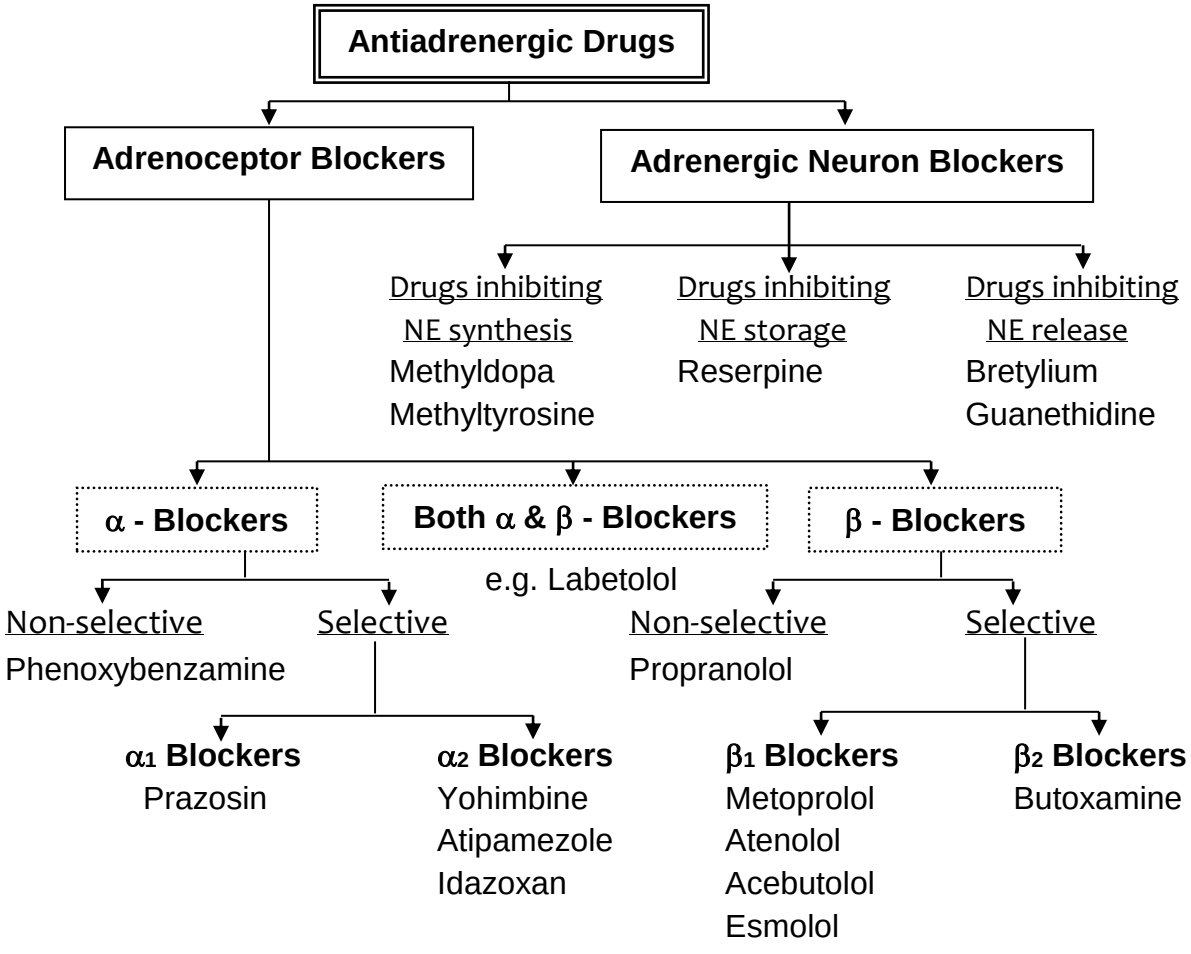
(2) Indirect acting adrenergic neuron blockers: These drugs do not block receptors; instead, they act presynaptically at the nerve terminal to cause a decreased release of the endogenous neurotransmitter norepinephrine.

The adrenergic neuron blockers interfere with the transmitter function of adrenergic neurons by the following mechanisms:

(i) *By interfering with the synthesis of catecholamines:* e.g. Methyldopa and methyltyrosine.

(ii) *By interfering with storage of norepinephrine:* e.g. Reserpine (It depletes NE stores in adrenergic neurons).

(iii) *By preventing the release of norepinephrine:* e.g. Guanethidine.



PHARMACOLOGICAL ACTIONS OF SYMPATHOLYTICS:

(1) CVS: Heart rate, force of cardiac contraction and cardiac output decreases.
[NB: The effect on a normal resting heart is not appreciable, but becomes prominent under sympathetic over-activity (exercise, vomition).**]**

(2) B.P.: Epinephrine reversal (net result - hypotension).

(3) Respiratory tract: Bronchoconstriction.

(4) Skeletal muscles: Relaxation.

(5) Eye: Reduces secretion of aqueous humour and intraocular tension. Thus, helpful in glaucoma.

ANTIADRENERGIC DRUGS AND THEIR CLINICAL USES:

α Blockers:

(1) α blockers (like Prazosin etc.) are used in human therapeutics as <u>vasodilators</u> in emergency control of dangerously high blood pressure or in peripheral ischaemic diseases.

(2) The ability of **α blockers** to reverse the effects of **xylazine** has now given these drugs a veterinary role.

- Atipamezole (α_2 blocker) selectively antagonizes medetomidine (α_2 agonist).
- Idazoxan (α_2 blocker) selectively antagonizes xylazine (α_2 agonist).
- Yohimbine is in general used as α_2 antagonist.

β - Blockers:

(1) **Pronethalol:** It was the first β blocker to be marketed. Although, effective in controlling arrhythmias and hypotension, it was found a carcinogen in mice and was later withdrawn.

(2) **Propranolol:** It is a non-selective β (β_1+β_2) antagonist.

- The drug is a competitive antagonist of isoprenaline at β adrenoceptors. Useful in angina pectoris and protects the heart from sympathetic drive.
- Inhibits the metabolic actions of adrenaline like muscle and liver glycogenolysis & lipolysis.
- Bronchoconstrictor and antiarrhythmic for heart.

(3) **Acebutolol, Metoprolol, Atenolol:** (Cardioselective β_1 blockers)

- Used for – **Angina pectoris**, **hypertension**, **cardiac arrhythmias** etc.

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Chapter - 9

Drugs acting on Autonomic Ganglia

DRUGS ACTING ON AUTONOMIC GANGLIA

GANGLIONIC TRANSMISSION:

Acetylcholine (ACh) is the primary excitatory neurotransmitter in both sympathetic and parasympathetic ganglia. Drugs alter the ganglionic function by either stimulating (ganglionic stimulants) or blocking (ganglionic blockers) the impulse transmission through the autonomic ganglia. The principal pathway of impulse transmission through the ganglia involves release of ACh from the preganglionic nerve endings and the stimulation of nicotinic receptors by ACh on the post-junctional membrane (EPSP) causing rapid depolarization and subsequent propagation of the impulse through the post-ganglionic nerve fibre.

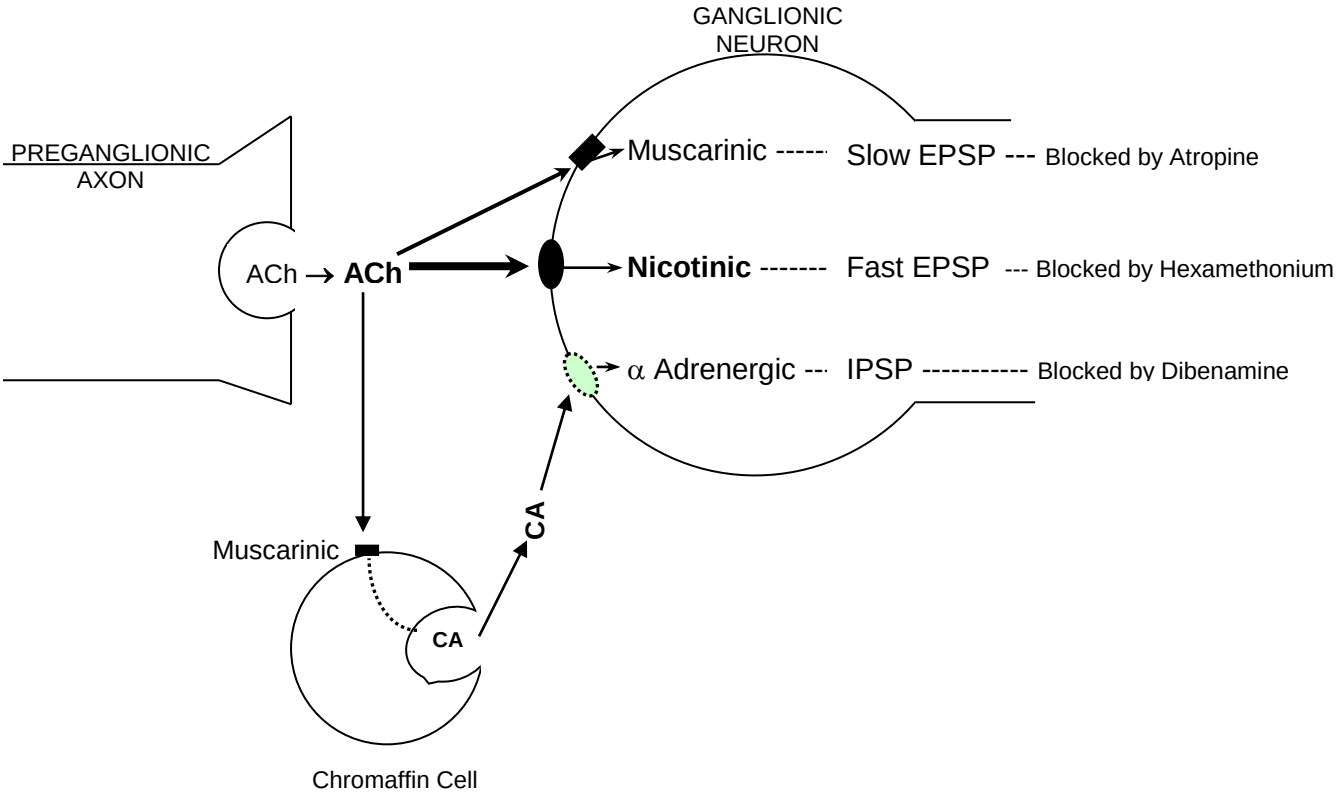

Figure: Impulse transmission in sympathetic autonomic ganglia.

ACh is discharged from the preganglionic nerve terminal and interacts with a nicotinic receptor on the ganglionic neuron to cause a rapid depolarization measured electrically as a fast excitatory post synaptic potential (EPSP). ACh also interacts with a muscarinic receptor on the ganglionic neuron to cause a delayed depolarization measured electrically as a slow EPSP. In addition, ACh activates nearby chromaffin cells through a muscarinic receptor, which results in a release of catecholamine (CA: dopamine or epinephrine). CA interacts with an α receptor on the ganglionic neuron to cause an inhibitory (hyperpolarization) response measured electrically as an inhibitory post synaptic potential (IPSP).

GANGLIONIC STIMULANTS:

The ganglionic stimulants stimulate the nicotinic receptors like ACh and cause EPSP and rapid depolarization.

(1) Natural Alkaloids:

(a) Nicotine: It is obtained from the leaves of *Nicotiana tabacum*. Small doses of nicotine stimulate the CNS. Large doses cause tremors or even convulsions. Respiratory stimulation is due to direct stimulation of medullary respiratory centre and through activation of carotid and aortic chemoreceptors. The stimulation is followed by depression of the CNS.

Nicotine can stimulate the sympathetic and parasympathetic ganglia in small doses. In large doses, it blocks ganglia.

The effects of nicotine on GI tract are due to stimulation of parasympathetic ganglia which include salivation, increase in tone and motility of GI tract and defaecation.

Nicotine toxicity may cause CNS excitation followed by marked depression and even death due to central respiratory failure and paralysis of peripheral respiratory muscles.

[NB: Nicotine transdermal has been therapeutically used for treatment of nicotine dependence and as an aid to smoking cessation.**]**

(b) Lobeline: It is obtained from the leaves of *Lobelia inflata*.

(2) Synthetic compounds:

(a) Trimethylammonium (TMA)
(b) Tetraethylammonium (TEA)
(c) Dimethylphenylpiperazinium (DMPP)

GANGLIONIC BLOCKERS:

These drugs competitively antagonize the action of ACh on the nicotinic receptors on the post-ganglionic membrane and thus block ganglionic transmission. Ganglionic blockers are all synthetic compounds.

(a) Hexamethonium
(b) Pentolinium
(c) Trimethaphan
(d) Mecamylamine

Pharmacological effects of Ganglionic Blockers:

(i) CVS: Vasodilatation, increased peripheral blood flow, venous pooling, decreased cardiac output, hypotension and tachycardia.
(ii) GI tract: Reduced tone and motility.
(iii) Eye: Mydriasis and cycloplegia.
(iv) Bladder: Relaxation and urine retention.
(v) Sweat glands: Anhydrosis.
(vi) Salivary glands: Xerostomia (dry mouth).

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Chapter – 10

Autacoids

AUTACOIDS

The term 'autacoid' is derived from Greek words – 'autos' meaning self and 'akos' meaning remedy or healing substance.

Autacoids are locally acting hormone like substances produced by a wide variety of cells in the body, having intense biological activity which act briefly at the site of synthesis and release (i.e. on adjacent cells).

Autacoids are also known as tissue hormones or local hormones. These are formed, released and inactivated within tissues. They are usually vasoactive and mediators of inflammation.

Autacoids differ from hormones in following ways:

(i) Hormones are produced by specific cells; and
(ii) They are transported through circulation to act on distant target tissues.

CLASSIFICATION OF AUTACOIDS:

(I) Classification based on chemical structure:

(1) Amine autacoids: Histamine, 5-Hydroxytryptamine (5-HT) or Serotonin.
(2) Lipid derived autacoids: Eicosanoids {Prostaglandins, Leucotrienes (LTs) and Thromboxanes (TXs)}, Platelet activating factor (PAF).
(3) Peptide autacoids: Plasma kinins (Bradykinin and Kallidin), Angiotensin, Vasoactive Intestinal Polypeptide (VIP) and Substance P.

(II) Classification based on origin:

(1) Precursor molecules in plasma: Bradykinin, Kallidin and Angiotensin.
(2) Preformed and stored in the cell: Histamine, 5-HT, VIP and Substance P.
(3) Precursor molecules in cell membrane phospholipids: Prostaglandins, LTs and PAF.

HISTAMINE = Tissue Amine

It is an amine present in a variety of animal tissues, venoms, bacteria and certain plants (e.g. stinging nettle). The amine is involved in inflammations, anaphylaxis, allergies and certain types of drug reactions, and it regulates gastric secretion.

SYNTHESIS, STORAGE AND CATABOLISM OF HISTAMINE:

Chemically, histamine is β-imidazolylethylamine. It is synthesized from the decarboxylation of amino acid histidine by a specific enzyme, histidine decarboxylase. This enzyme is present in all cell types that contain histamine.

Histamine is widely distributed throughout mammalian tissues. It is generally accepted that most of histamine stored within the body is synthesized locally. Dietary histamine and histamine produced by enteric bacteria are disposed off rapidly after absorption into the portal circulation and contribute little or nothing to tissue storage sites.

In the animal body, histamine (basic) is found complexed with heparin (acidic) and protein in the granules of mast cells.

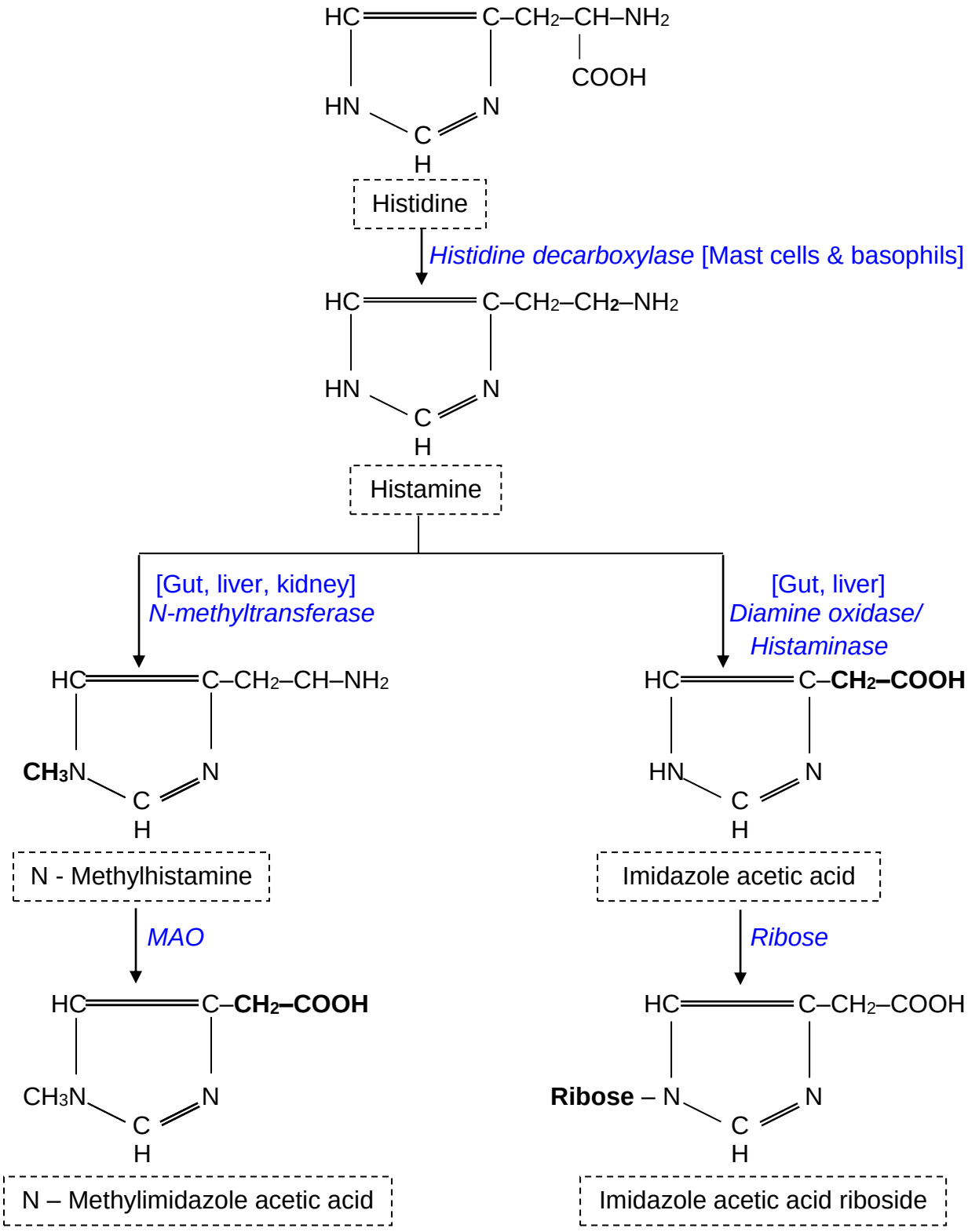


Figure: Showing pathway of histamine synthesis and metabolism in animals.

Two general stores of histamine are there in mammals – one is mast cell pool and the other is non-mast cell pool.

Mast cell pool	Non-mast cell pool
(i) Made up of mast cells (connective tissue) and basophils (blood).	(i) Made up of histaminocytes localized in GI tract, CNS, dermis and other organs.
(ii) Turnover of histamine is slow.	(ii) Fast turnover.
(iii) The mast cell pool represents the histamine that participates in inflammatory responses, allergic phenomena, shock, some adverse drug reactions and other forms of cellular insult.	(iii) It is synthesized and released continuously rather than being stored. Functions: CNS – Neurotransmitter GIT – Control of gastric secretion.
(iv) Effect of histamine liberating drug 48/80 – complete emptying of storage granules & release of histamine.	(iv) Resistant to histamine releasing drugs such as compound 48/80.

The catabolism of histamine includes ring methylation (to form N-methylhistamine) catalyzed by N-methyltransferase and oxidative deamination catalyzed by diamine oxidase (histaminase) forming imidazolylacetic acid and its riboside. The metabolites of histamine are pharmacologically inert and are excreted in urine.

HISTAMINE RECEPTORS:

Histamine receptors have been classified into three types as H_1, H_2 and H_3 receptors. The important features of the three types are presented in the following table:-

	H_1	H_2	H_3
Selective Agonist	2-methylhistamine	4-methylhistamine	α-methylhistamine
Selective Antagonist	Chlorpheniramine	Ranitidine	Thioperamide
Distribution In The Body And Actions Mediated	• Smooth muscle (GIT, RT & uterus): Contraction. • Blood vessels: Endothelium-Vasodilatation & increased capillary permeability. Smooth muscle-Vasoconstriction. • Afferent nerve endings: stimulation (itching & pain) • Ganglionic cell: Stimulation. • Adrenal medulla: Release of catecholamines • Brain: Transmitter function.	• Gastric glands: Acid secretion. • Blood vessels: Dilatation. • Heart: +ve inotropy +chronotropy • Brain: Transmitter function.	• Brain: Inhibition of histamine release (sedation). • Lung, spleen, skin, gastric mucosa: ↓ histamine content. • Primarily serves as **autoreceptors** controlling histamine release from neurons in brain.

PATHOPHYSIOLOGICAL FUNCTIONS OF ENDOGENOUS HISTAMINE:

1. Histamine has dominant physiological role in mediating secretion of HCl in the stomach.
2. Histamine is released from the mast cells following Antigen - Antibody interactions during hypersensitive reactions (Type-1 hypersensitivity).
3. Histamine serves as a neurotransmitter in parts of CNS that regulate water intake, body temperature, release of anti-diuretic hormone (ADH), blood pressure and pain perception.
4. Histamine is a passive regulator of GI tone and motility which helps to maintain normal peristalsis.
5. Histamine is released whenever there is extensive tissue damage. It mediates local circulatory response to injury and inflammatory reactions.
6. Histamine is considered to play an essential role in the process of tissue growth and repair because these tissues contain high concentrations of histamine.

HISTAMINE RELEASE:

Various factors are responsible for release of histamine from mast cells –

(i) Tissue damage by trauma, stings, venoms, proteolytic enzymes etc.
(ii) Antigen – antibody reactions involving IgE antibodies.
(iii) Some drugs like tubocurarine, morphine, atropine, polymyxin B, vancomycin etc. release histamine without an immunological reaction.

PHARMACOLOGICAL EFFECTS OF HISTAMINE:

(1) Blood Vessels: Histamine causes marked dilatation of smaller blood vessels including arterioles, capillaries and venules. However, it causes a constrictor effect on large blood vessels. In rabbits, histamine is a “pressor agent” as a result of pronounced constriction of blood vessels.

Histamine Shock:

The intense dilatation of capillary bed is accompanied by increase in capillary permeability. In the presence of histamine, the capillary endothelial cells constrict exposing the membrane (gap at the junctions), which is freely permeable to plasma along with its proteins decreasing the blood volume. The dilated arterioles, capillaries and venules that tag large volumes of blood and reduce venous return to heart and thus the cardiac output. These effects are precipitated by histamine release during allergic or anaphylactic reactions in sensitive individuals. The condition may cause death due to vascular shock as seen in acute surgical or haemorrhagic shock.

Triple Response:

Histamine produces a characteristic triple response in skin following intradermal injection. It consists of the following:-

A localized red spot – due to intense capillary dilatation developing within a few seconds and attaining maximum hue within a minute.

Wheal – Localized oedema fluid forming a wheal in about 90 seconds due to exudation of fluid from capillaries and venules; and

Flare (Diffuse redness) – i.e. redness in the surrounding area due to arteriolar dilatation mediated by axonal reflex.

(2) Non-vascular smooth muscles: Histamine causes acute bronchial constriction (via H_1 receptors) in most of the species. However, guinea pigs are exceptionally sensitive and even minute doses of histamine can evoke bronchoconstriction leading to death.

Histamine causes tracheal relaxation in cat (both H_1 & H_2), bronchial relaxation in sheep (H_2) and uterine relaxation in rat (H_2) but uterus is generally contracted in other species.

(3) Exocrine glands: Increased gastric acid secretion (due to H_2 receptors).

(4) Sensory nerve endings: Itching and pain due to stimulation of nerve endings.

(5) Autonomic ganglia and adrenal medulla: Release of adrenaline and rise of blood pressure.

(6) C.N.S.: Histamine does not penetrate blood brain barrier.

MEDICAL USES OF HISTAMINE:

Histamine has no therapeutic application, but used in experimental pharmacology. Clinical applications in human include –

(i) Use of histamine as a test agent for achlorhydria.
(ii) Used in diagnosis of phaechromocytoma, and
(iii) Used for production of triple response to evaluate integrity of sensory innervations and circulatory competency.

ANTIHISTAMINES:

These are drugs used to antagonize the effects of histamine liberation. The antihistamines act as competitive antagonists of histamine at receptor sites.

The antihistamines of clinical value in veterinary medicine are H_1 antagonists.

H_1 ANTAGONISTS:

These are the drugs which competitively antagonize actions of histamine at H_1 receptors. These are also known as *Conventional Antihistaminics.* The classification of H_1 antagonists has been detailed as below:

Drug	Trade Name	Dose
First Generation		
(1) Ethanolamines:		
Diphenhydramine HCl	Benadryl (Parke-Davis)	LA – 0.5 to 1.0 mg/kg orally/i.v. bid SA – 1 to 2 mg/kg orally/i.v. bid
(2) Ethylene diamines:		
Pyrilamine maleate	Histosol	LA &SA–1 to 2 mg/kg i.m., i.v., s.c.
(3) Alkylamines:		
Chlorpheniramine maleate	Jeet (Alembic), Anistamin (Intas)	LA – 0.1 to 0.2 mg/kg i.m., i.v. SA – 0.4 to 0.6 mg/kg i.m., i.v.
Pheniramine maleate	Avil (Intervet)	-- do --
(4) Piperazines:		
Hydroxyzine HCL	Atarax (UCB Pharma)	25 to 100 mg total dose (man)
(5) Phenothiazines:		
Promethazine HCl	Phenergan (Rhone Poulenc)	LA &SA – 0.5 to 1 mg/kg oral, i.m., i.v., s.c
(6) Piperidines:		
Cyproheptadine HCl	Practin (Merind)	12 - 16 mg/adult (man) in divided doses

Second Generation		
(1) Piperazines:		
Cetirizine HCl	Cetzine (Glaxo)	5–10 mg (single adult total dose in man)
(2) Piperidines:		
Loratadine HCl	Loridin (Cadila)	10 mg (single adult total dose in man)
Fexofenadine HCl	Allegra (Hoechst)	60 mg (single adult total dose in man)
Terfenadine HCl	Terin (Wockardth)	60-80mg(single adult total dose in man)

Out of the above classification, diphenhydramine, promethazine & hydroxyzine are highly sedative; pheniramine and cyproheptadine are moderately sedative and chlorpheniramine and pyrilamine are mildly sedative while second generation antihistaminics do not possess CNS depressant property.

Cetirizine: It is a metabolite of hydroxyzine (1st generation antihistaminic) with marked affinity for peripheral H_1 receptors. It penetrates blood brain barrier poorly, so is very less sedative. It attains high and longer lasting concentration in skin, which may be responsible for its superior efficacy in urticaria/ atopic dermatitis. It is indicated in upper respiratory allergies, pollinosis, urticaria and atopic dermatitis; also used as adjuvant in seasonal asthma.

Cyclizine, meclizine, promethazine, diphenhydramine (Anti- motion sickness): These agents have prophylactic value in milder types of motion sickness; should be taken one hour before starting journey. Promethazine can also be used in morning sickness, drug induced and post-operative vomiting, radiation sickness. [H_1 receptors mediate emesis in emetic centre.]

Clinical uses of H_1 blockers:

(i) In allergic and anaphylactic reactions.
(ii) In bronchial asthma, laminitis, azoturia and pulmonary emphysema in horses.
(iii) In asthma, bloat, acetonaemia, gangrenous mastitis, metritis and retained placenta.
(iv) In the treatment of skin affections like dermatitis, pruritis and eczema (their mild local anaesthetic action helps in pruritis).

[NB: Sodium cromoglycate: The drug is used for prevention of asthma in man. It acts by stabilizing pulmonary mast cells sensitized to the antigen and prevent the release of histamine. It is neither an antihistaminic nor smooth muscle relaxant. The drug inhibits activation of Ca^{2+} entry in sensitized mast cells thereby preventing release of histamine. So, the drug is used prophylactically by inhalation.**]**

H_2 ANTAGONISTS:

These drugs block the effects of histamine that are mediated through H_2 receptor stimulation, such as increase in gastric acid secretion and increase in heart rate and automaticity of auricles and ventricles. The H_2 antagonists also act as competitive antagonists of histamine for H_2 receptors. The H_2 antagonists include – cimetidine, ranitidine, famotidine, roxatidine, nizatidine etc. These drugs are of value in the treatment of peptic ulcer in man and animals.

5-HYDROXYTRYPTAMINE (5-HT) or SEROTONIN

≅ Enteramine or Vasotonin

Serotonin was the name given to the vasoconstrictor substance which appeared in serum when blood clotted. Enteramine was the name given to the smooth muscle contracting substance present in enterochromaffin cells of gut mucosa.

SOURCE:

5-HT is formed and localized in three essential pools in the body:

(i) Enterochromaffin cells of intestine (about 90%).

(ii) Small number of neurons in CNS and mast cells of rodents (rat, mice, hamsters) along with histamine and heparin.

(iii) Blood platelets.

In addition to the endogenous 5-HT reserve, it is also found in invertebrates and plants (banana, pear, pineapple, tomato, stinging nettle etc).

In the pineal gland, 5-HT is converted to melatonin after acetylation and methylation.

ROLE OF ENDOGENOUS 5-HT:

(i) Neurotransmitter in brain in tryptaminergic nerves. Its deficiency causes depression and excess causes excitement.

(ii) It is a precursor molecule of melatonin hormone.

(iii) It helps to regulate the tone and motility of gastrointestinal tract.

(iv) Platelet 5-HT serves as one of the mediators of blood clot formation.

SYNTHESIS AND DESTRUCTION OF 5-HT:

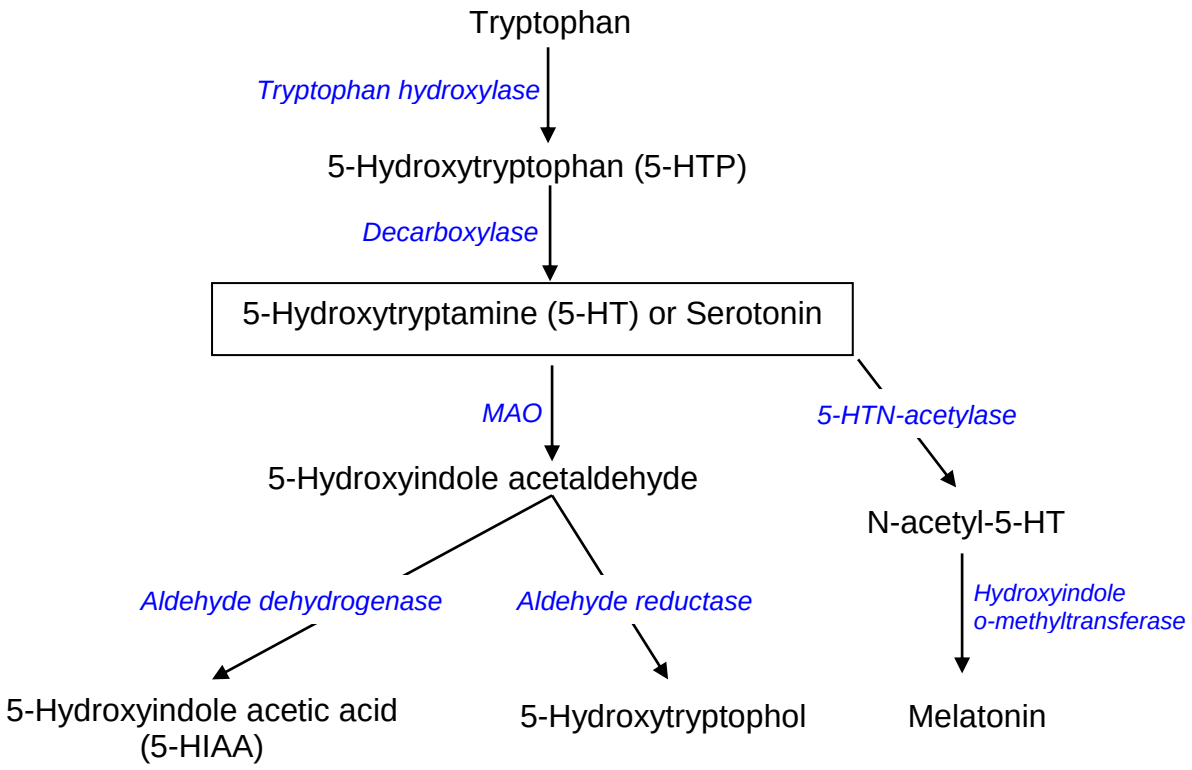


Fig.: Showing synthesis and degradation of 5-HT

5-HT is synthesized from dietary tryptophan in a two stage chemical reaction:-

(i) Tryptophan is hydroxylated by the enzyme tryptophan-5-hydroxylase to give 5-hydroxytryptophan (5-HTP).

(ii) 5-HTP is then decarboxylated to yield 5-HT.

Like catecholamines, 5-HT is also stored in storage granules and its uptake is also inhibited by Reserpine. Enzymes like MAO, dehydrogenase and aldehyde reductase help to metabolize 5-HT.

5-HT RECEPTORS:

Four families of 5-HT receptors (5-HT_1, 5-HT_2, 5-HT_3 and 5-HT_{4-7}) comprising of **14** receptor subtypes have so far been recognized.

(1) 5-HT_1 {Five subtypes i.e. 5-$HT_{1A, 1B, 1C, 1D, 1E}$}**:** Autoreceptors; inhibit serotonergic neural activity in brain. Functions are neural inhibition and vasoconstriction.

(2) 5-HT_2 {Three subtypes i.e. 5-$HT_{2A, 2B, 2C}$}**:** CNS and peripheral sites (esp. vascular and visceral smooth muscles, platelets and ANS neurons). Effects are vasoconstriction, intestinal, bronchial and uterine contraction and platelet aggregation.

(3) 5-HT_3 {No subtype}**:** Peripheral Nervous System – Emesis, gut peristalsis, bradycardia, transient hypotension, apnoea, pain, itching etc.

(4) 5-HT_{4-7}:

(i) 5-HT_4: (No subtype) Enteric nervous system. Mediate intestinal secretion and augments peristalsis.

(ii) 5-HT_5: Two subtypes i.e. 5-$HT_{5A, 5B}$.

(iii) 5-HT_6: No subtype.

(iv) 5-HT_7: No sybtype.

} Not much is known about 5-HT_{5-7} .

PHARMACOLOGICAL EFFECTS OF 5-HT:

(1) C.V.S.: Vasoconstriction on major arteries and veins. Vasodilatation is seen in capillaries due to activation of 5-HT receptors in endothelial cells and local release of EDRF and prostaglandins.

Rapid intravenous infusion of 5-HT produces a **triphasic response**:-

(a) An initial fall of systemic arterial blood pressure accompanied by paradoxical bradycardia caused mainly by reflex chemoreceptor stimulation (Bezod – Jarisch Effect).

(b) A short period of pressure effect (similar to epinephrine effect); and

(c) A prolonged fall in systemic blood pressure attributed to a vasodilator effect in the vascular bed of skeletal muscle.

(2) Gastrointestinal tract (GIT): 5-HT increases motility of small intestines and inhibits the motility of stomach and large intestines.

(3) Respiratory tract (RT) and Uterus: Constriction of bronchi and uterine contraction.

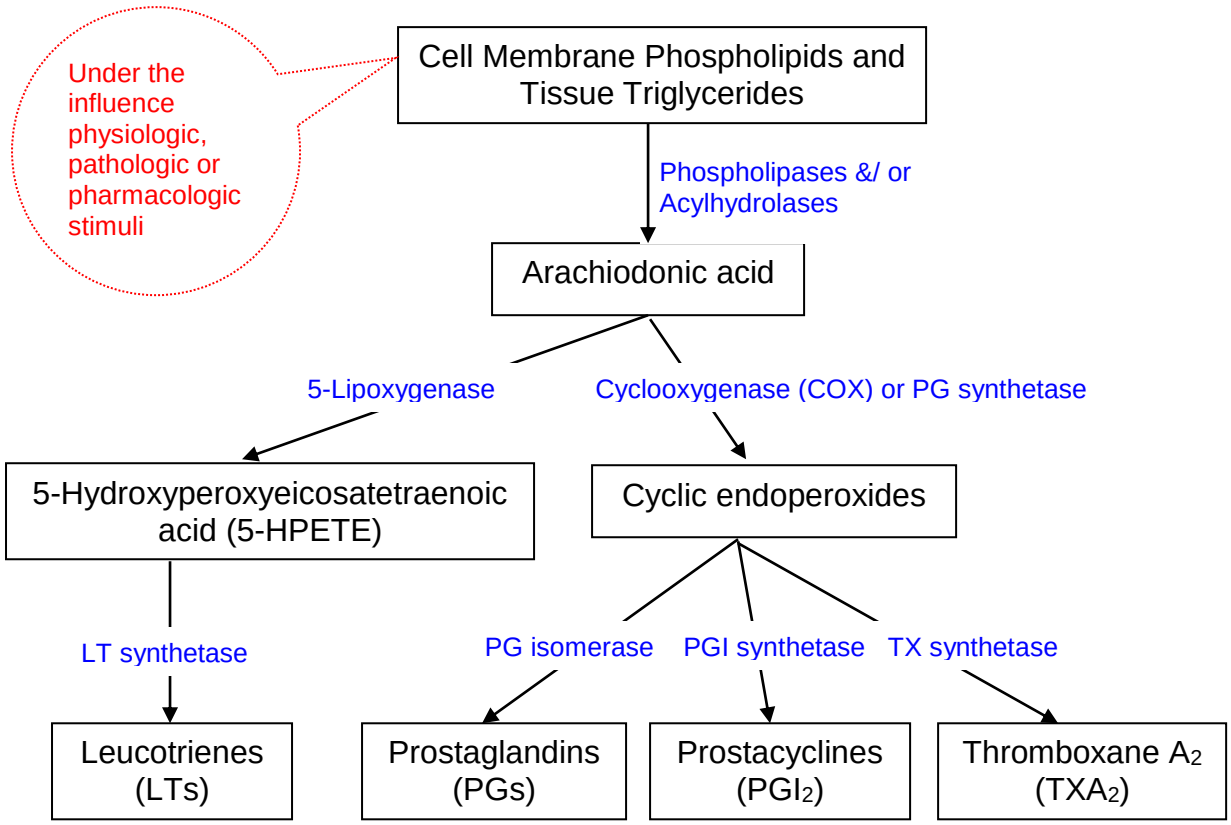
5-HT ANTAGONISTS:

LSD, ergot alkaloids, methysergide, cyproheptadine (antiallergic and antipruritic; appetite enhancer in children and helps to gain body weight – 5-HT has negative effect on hunger centre and positive effect on growth hormone secretion), ketanserin, clozapine (effective in schizophrenia), risperidone etc. The therapeutic value of 5-HT antagonists in veterinary medicine is not yet established.

EICOSANOIDS

The biologically active substances that are derived from 20 carbon polyunsaturated fatty acids (mainly arachiodonic acid) which share a prefix 'eicosa' (means twenty) are termed eicosanoids. These include prostaglandins (PGs), prostacyclins (PGI_2), thromboxane (TXA_2) and leucotrienes (LTs).

SYNTHESIS OF EICOSANOIDS:

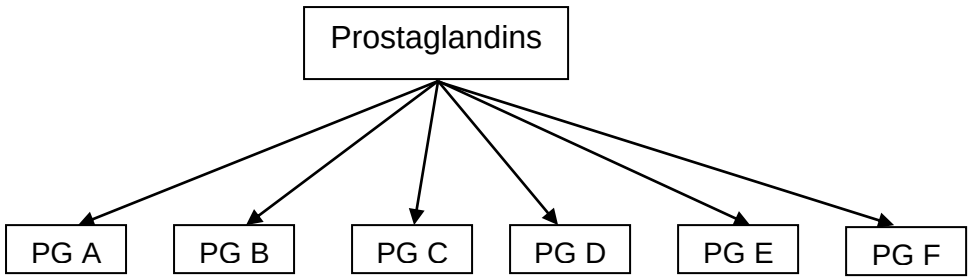


Every cell in the body is capable of synthesizing eicosanoids. The first step in their formation is release of arachiodonic acid from the phospholipids of cell membrane and tissue triglycerides by the action of the enzymes phospholipases and acylhydrolases. Several factors are associated with activation of these enzymes which include physiological, pharmacological and pathological stimuli. Other autacoids like angiotensin and kinins activate acylhydrolases and promote PG synthesis. The sequence of formation of eicosanoids has already been shown above.

PROSTAGLANDINS:

Two American Gynaecologists, Kurzrok and Lieb, in 1930, reported that human semen contained a substance which was found to contract isolated uterine and other smooth muscle strips and caused a fall in blood pressure in animals. The active principle was termed 'prostaglandin', thinking that it was derived from prostate gland.

Classification of Prostaglandins:



The above classification of PGs is according to substituents on the cyclopentane ring of prostaglandin molecule. Some newer PG related compounds are PGG, PGH, PGI (prostacyclin) and thromboxane.

The PGs are further categorized as mono, di or triunsaturated depending on the number of double bonds in the side chains. This classification appears as a subscript to the letter.

Examples are –

PGE_1 contains one double bond.

PGE_2 contains two double bonds.

PGE_3 contains three double bonds.

Cyclooxygenase (COX):

This enzyme is widely distributed in mammals and it helps in metabolizing arachiodonic acid to its PG derivatives.

There are two major isoforms of cyclooxygenase i.e. cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is constitutive. It serves to synthesize the small amounts of PGs that participate in normal physiologic functions. It is especially important in producing those eicosanoids that have protective actions on GI mucosa. Inhibition of COX-1 activity can therefore be detrimental to the patient because of loss of GI protection of mucosal epithelial cells.

The other isoform of cyclooxygenase is COX-2. It is not constitutive; rather it is inducible in nature. When cells are exposed to bacterial lipopolysachharide and certain inflammatory cytokines & growth factors, the synthesis of COX-2 is induced. The inducible COX-2 results in concentrations of PGs that participate in inflammatory reactions.

PROSTACYCLIN (PGI_2):

It is a potent vasodilator and exerts antiaggregatory activity on blood platelets. PGI_2 has a very brief half life of 2-3 minutes.

THROMBOXANE A_2:

It is synthesized in platelets (thrombocytes). Thromboxane A_2 plays an important physiological role as a vasoconstrictor and proaggregatory in thrombus formation.

LEUCOTRIENE:

It is synthesized in lung, platelets and white blood cells by metabolism of arachiodonic acid via lipoxygenase pathway. Leucotrienes are thought to be chemotactic in nature for leucocytes and participate in inflammatory responses.

FUNCTIONS OF EICOSANOIDS:

(i) Prostacyclin acts as an antagonist of prostaglandins and thromboxane A_2 on blood platelets.

(ii) Prostaglandins and prostacyclins promote vasodilatation and regulate the tone of vasculature and control blood flow in the vital organs, possibly by counteracting the circulatory vasoconstrictor autacoids. TXA_2 is a potent vasoconstrictor.

(iii) Prostaglandins and leucotrienes along with other autacoids are released during allergic reactions and contribute to the bronchoconstriction and other signs.

(iv) Prostacyclin controls renal blood flow, urine formation, renin secretion and checks the action of ADH.

(v) Presence of prostaglandins in semen may have a role in facilitating conception following coitus. They may also help in termination of pregnancy at the term. $PGF_{2\alpha}$ elaborated by uterus (mare, cow, sow & ewe) functions like luteolytic hormone and is used for synchronizing oestrous. Aspirin inhibits uterine contractions during parturition by interfering with prostaglandin synthesis.

(vi) Inflammation: The formation of prostaglandins and leucotrienes is enhanced by tissue injury (mechanical, chemical, thermal or infectious) which are responsible for reactions of inflammations (along with other autacoids), such as increase in vascular permeability, oedema and leukocyte infiltration and potentiate the pain inducing effect of bradykinin. Leucocytes release leucotrienes which help in migration of leucocytes.

CLINICAL USES OF EICOSANOIDS:

(i) In veterinary practice, $PGF_{2\alpha}$ analogues [like Dinoprost (Lutalyse® - Novartis), Tiaprost (Iliren® - Intervet) etc.] are used for:-
   (a) Oestrous synchronization (cow, ewe, goat, buffalo etc.)
   (b) Induction of oestrous in anoestrous animals.
   (c) Expulsion of mummified foetus; and
   (d) Expulsion of pus in pyometra.

(ii) Therapeutic abortion in human females – PGE_2 analogue (Dinoprostone) is used for abortion during first trimester.

(iii) Impotency – PGE_1 analogue (Alprostadil) may be used in the treatment of impotency.

(iv) Maintenance of patent Ductus Arteriosus: PGE_1 analogue (Alprostadil) is used in the treatment of congenital malformations of the heart in neonates.

PLATELET ACTIVATING FACTOR (PAF)

PAF is another autacoid derived from membrane phospholipids, and is therefore related to the eicosanoid family. Whereas the eicosanoids are formed from a wide variety of cell types, PAF is synthesized principally by platelets, endothelial cells and circulating leucocytes.

FUNCTIONS:

(i) Mediator of thrombin-induced platelet aggregation (by forming TXA_2).

(ii) Contributes to the reactions of inflammation (increased vascular permeability, oedema, pain, infiltration of leucocytes and release of lysosomal enzymes). PAF is the most potent agent known to increase vascular permeability.

(iii) Although PAF lowers blood pressure due to its relaxing effect on vascular smooth muscle, it markedly contracts smooth muscle of the gut, stomach, uterus and peripheral airways of the lungs.

(iv) PAF is considered to be one of the most active endogenous activators of prostaglandins and related eicosanoids. Thus, biological roles of PAF are often linked to those exhibited by the eicosanoid family.

(v) May have a role in ovulation, implantation and parturition. **In absence of PAF, ovulation does not occur.** After fertilization, the embryo produces PAF which helps in implantation of the blastocyst. At the time of parturition, PAF aids in increasing uterine contractions. Just before parturition, PAF is found in the amniotic fluid (released from foetal lungs).

Despite the wealth of physiologic and pathophysiologic activities proposed for PAF, pharmacologic manipulation of PAF synthesis and receptors is at a preliminary stage. The clinical significance of PAF antagonists is currently unknown for veterinary medicine.

CYTOKINES

In response to certain inflammatory and immunological stimuli, many types of mammalian cells produce one or more of a variety of small proteins termed cytokines. Cytokines have a vital role in the initiation and regulation of various inflammatory and immunological responses. The important cytokines include:

(i) Tumour necrosis factor-α (TNF-α)

(ii) γ-Interferon, and

(iii) Interleukins (ILs).

Currently, monoclonal antibodies raised against these specific proteins represent the primary pharmacotherapeutic intervention relevant to the area of cytokines. However, because of likely future importance of cytokines to pharmacologic management of bacterial invasion and other inflammatory conditions, it has been discussed here.

POLYPEPTIDES

The pharmacologically active polypeptides include –

1. Angiotensins
2. Kinins
3. Substance P and
4. Vasoactive Intestinal Polypeptide (VIP).

The polypeptides have a variety of extremely potent effects.

ANGIOTENSINS:

Angiotensin is a blood borne polypeptide that serves as a circulating link between the kidney and systemic haemodynamic control systems. It is formed from angiotensinogen. It exists as angiotensin I, angiotensin II and angiotensin III. The sequential formation of angiotensins are shown below –

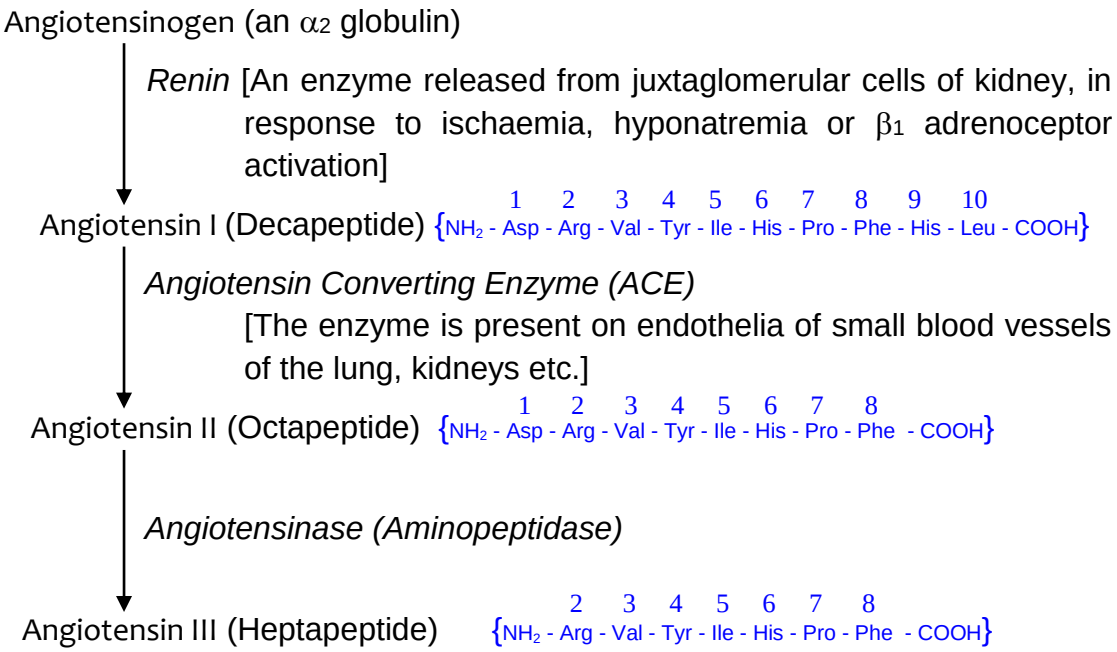


Figure: Sequential formation of angiotensin I, II and III. The structure of angiotensin shown is that found in the rat, pig, horse and human. Bovine angiotensin contains valine in position 5.

Previously, the peptide angiotensin was 'hypertensin' or 'angiotonin' until 1958 when the compromise term angiotensin was adopted. Angiotensin II is a powerful vasoconstrictor having 40 times the potency of NE and causes blood pressure to rise due to direct action on vascular smooth muscles.

Angiotensin is not a mediator of inflammation. It is discussed here because of its chemical relationship to the kinins. Its activation is terminated rapidly in blood. Its half life is less than one minute.

Renin Angiotensin System:

The system has homeostatic role in maintaining haemodynamics and water and sodium balance. The first step in the function of this system is secretion of renin from the juxtaglomerular cells, which is stimulated by renal as well as extrarenal factors. The renal factors include reduced renal blood flow (lowered blood volume and/or blood pressure) and lowered Na^+ concentration in upper tubular fluid. The extrarenal component comes from enhanced sympathetic outflow as a result of reduced blood volume, cardiac output and blood pressure, causing release of NE from sympathetic nerve endings. NE activates β_1 adrenergic receptors on juxtaglomerular cells causing renin secretion. Prostacyclin also causes release of renin. Renin accelerates formation of angiotensins, which cause intense vasoconstriction and increase in blood pressure. Angiotensin also promotes aldosterone secretion, which helps in Na^+ retention and increase in the volume of extracellular fluid. The vasoconstriction also contributes to Na^+ retention. The antagonists of the system [Angiotensin Converting Enzyme (ACE) antagonists] are used as vasodilators in renal hypertensive human subjects (captopril, enalpril etc.).

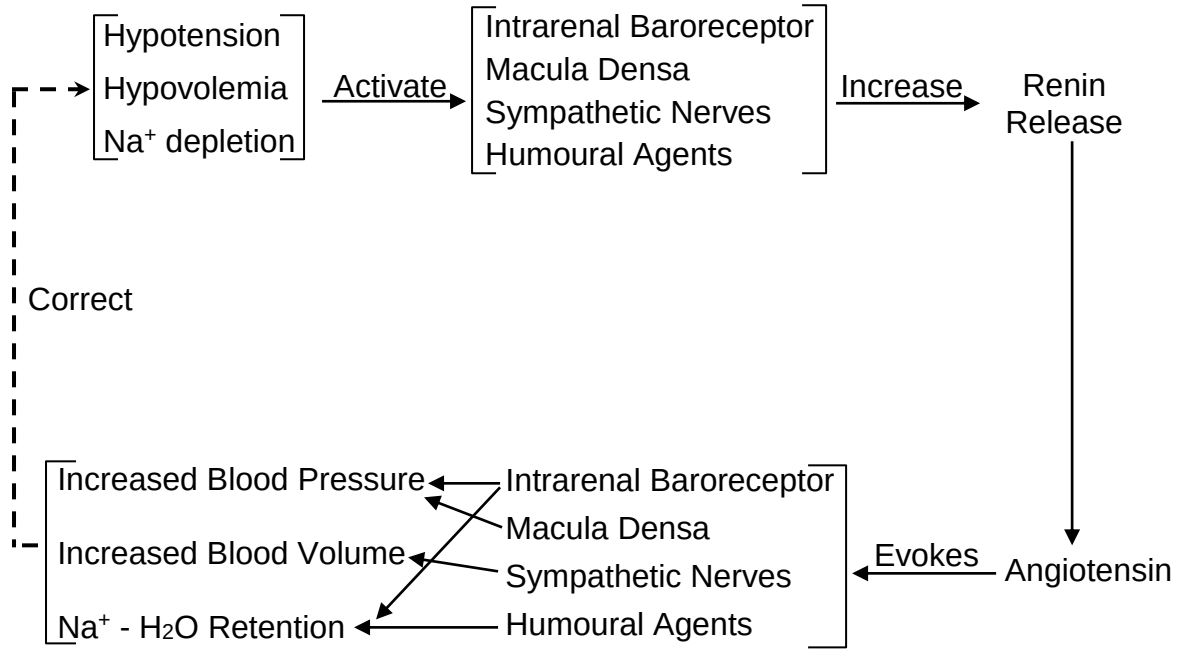


Figure: Haemodynamic interrelationship of the renin – angiotensin system.

PLASMA KININS:

These include Bradykinin and Kallidin, which have a role in mediating pain (nociception) and inflammatory responses and in regulating blood pressure, haemodynamics and fluid & electrolyte balance. Bradykinin is a nonapeptide while Kallidin is a decapeptide.

Prekallikreins (found in plasma, GIT and pancreas) are activated to kallikreins by the Hageman factor (factor XII) or plasmin, and others such as tissue damage, contact with glass, collagen and skin, pH changes etc. which disrupt normal haemodynamics. The kallikreins are present in plasma, exocrine glands (pancreas & salivary) and other organs. These are proteinases which convert a high molecular weight kininogen to bradykinin and a low molecular weight kininogen to Kallidin.

Kallikrein – kininogen – kinin system:

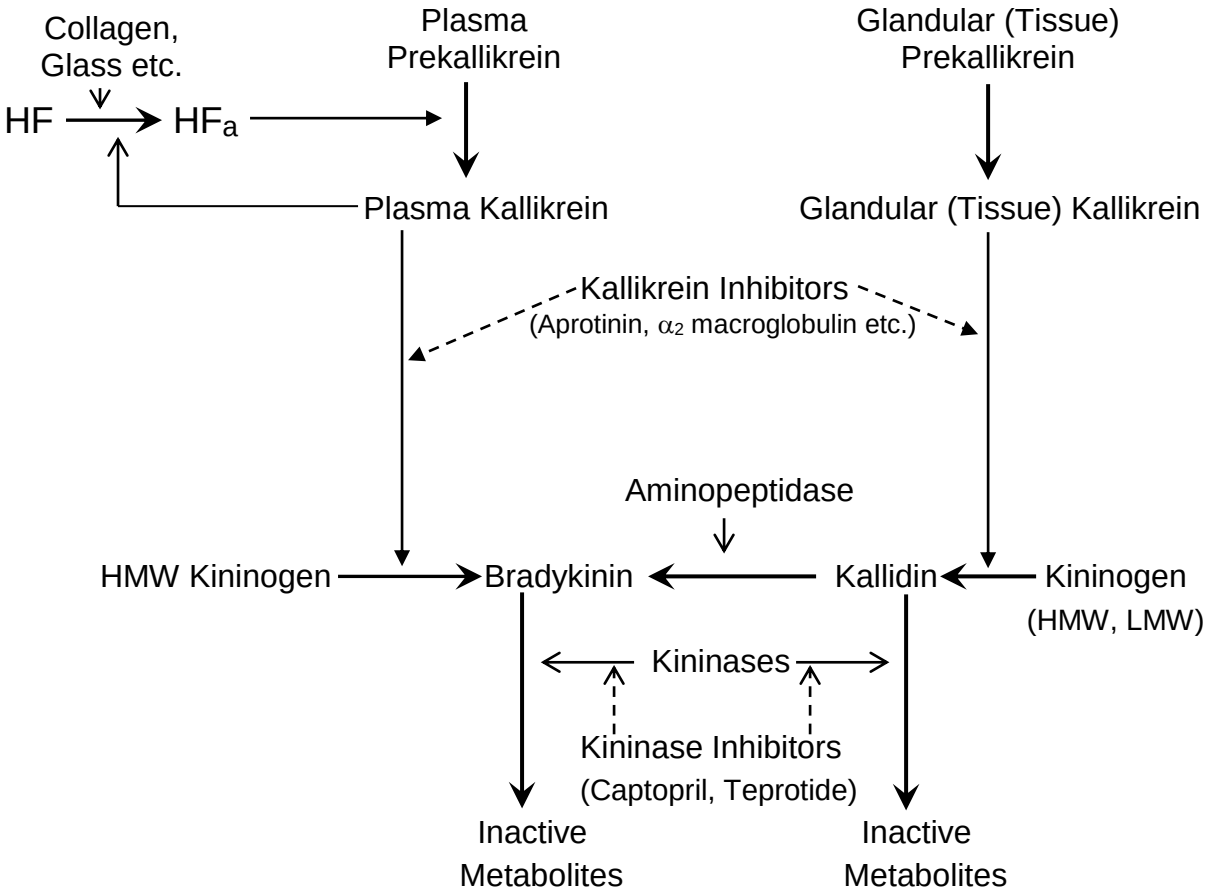


Figure: Formation and inactivation of kinins. HF = Hageman factor, HF_a = activated HF, HMW LMW = high and low molecular weight. Wide solid lines represent conversion of substrate to product. Narrow solid lines represent enzymic acceleration of substrate conversion to product. Dashed lines represent sites of inhibitory actions.

Pathophysiological and pharmacological actions of kinins:

(1) The kinins are responsible for production of pain sensation during tissue injury.
(2) They cause hypotension (about 10 fold more potent than histamine) following marked peripheral vasodilatation and increase in permeability in the minute blood vessels with oedema formation as seen with histamine.
(3) The kinins also mediate inflammatory responses.
(4) They cause constriction of non-vascular smooth muscles (intestine, uterus, bronchi) causing pain.
(5) Renal effects of kinins are opposite to those of renin angiotensin system (increase of urine volume and excretion of Na^+).

VASOACTIVE INTESTINAL POLYPEPTIDE (VIP)

VIP is present in small intestine and also widely distributed in peripheral nerves and the CNS. Although, VIP exerts multiple pharmacological actions in different tissues, its physiologic relevance remains questionable.

SUBSTANCE P

Substance P was first extracted from horse intestine and brain; it is an endecapeptide. It has some bradykinin like action and is a potent stimulator of the gut.

Apart from VIP and substance P, several other vasoactive peptides of which the actions in pathophysiologic states are less known, are Eledoisin, Physalamin, Coerulein, Colostrokinin, Urokinin and kinins of wasp and hornet venoms.

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