Chapter ... 8

NEUROHUMORAL TRANSMISSION, CO-TRANSMISSION AND CLASSIFICATION OF NEUROTRANSMITTERS

♦ **LEARNING OBJECTIVES** ♦

After completing this unit, reader should be able to:

- Describe Physiological Steps Involved in Neurohumoral transmission and Co-transmission.
- Describe importance neurotransmitters of autonomic nervous system.

8.1 INTRODUCTION

Neurohumoral transmission refers to the transmission of impulse through synapse and neuro-effector junction by the release of humoral (chemical) substances. The term 'conduction' stands for the passage of an impulse along an axon or muscle fibres. The transmission of a nervous impulse from neuron to neuron or from neuron to effector organ by means of a neurohumoral substance.

Neurotransmiter are endogenous chemicals that enable neurotransmission. It is a type of chemical messenger which transmits signals across a chemical synapse, such as a neuromuscular junction, from one neuron to another target neuron, muscle cell, or gland cell.

The principal neurotransmitters released from the postganglionic sympathetic and parasympathetic nerve endings respectively are noradrenaline (NA or norepinephrine, NE) and acetylcholine (ACh), whereas the transmitter released in ganglia from the preganglionic nerve ending of both systems is acetylcholine.

Almost all autonomic drugs, which are used clinically, exert their pharmacological actions by altering essential steps in the neurohumoral transmission process. There are a number of other neurotransmitters, which are called as non-adrenergic non-cholinergic transmitters,

released from the specific nerve endings. Those include nitric oxide, serotonin (5-HT), ATP, dopamine, GABA, purines, peptides etc.

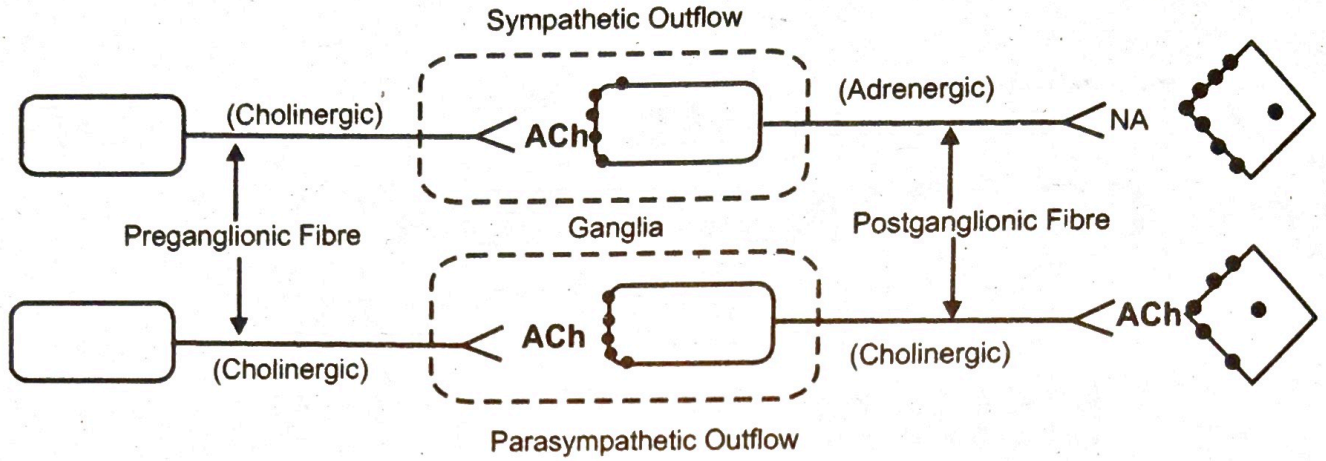

Fig. 8.1: Sympathetic and parasympathetic outflow

Preganglionic Neuron:

In the autonomic nervous system (ANS), fibres from the central nervous system to the ganglion are known as preganglionic fibres. All preganglionic fibres, whether they are in the sympathetic nervous system (SNS) or in the parasympathetic nervous system (PSNS), are cholinergic; these fibres use acetylcholine as their neurotransmitter and are myelinated.

Autonomic ganglia are clusters of neuronal cell bodies and their dendrites. They are a junction between autonomic nerves originating from the central nervous system and autonomic nerves innervating their target organs in the periphery.

Postganglionic Neuron:

In the autonomic nervous system, fibres from the ganglion to the effector organ are called postganglionic fibres. The post-ganglionic neurons are directly responsible for changes in the activity of the target organ via biochemical modulation and neurotransmitter release.

The neurotransmitters used by postganglionic fibres differ in the parasympathetic division. They are cholinergic and use acetylcholine as their neurotransmitter. In the sympathetic division, most are adrenergic, meaning they use norepinephrine as their neurotransmitter.

Synapse is the site of transmission of electric nerve impulses between two nerve cells (neurons) or between a neuron and a gland or muscle cell (effector). A synaptic connection between a neuron and a muscle cell is called a **neuromuscular junction**.

Effector organs are smooth muscle, cardiac muscle and glands that respond to nerve impulses from the central nervous system without conscious thought. They are part of the automatic, or involuntary, nervous system, along with receptors, afferent nerves and efferent nerves.

8.2 PHYSIOLOGICAL STEPS INVOLVED IN NEUROHUMORAL TRANSMISSION

The sequence of events involved in neurotransmission is of particular importance pharmacologically, since the actions of most drugs modulate the individual steps. The term conduction is reserved for the passage of an impulse along an axon or muscle fibre; transmission refers to the passage of an impulse across a synaptic or neuroeffector junction.

Axonal Conduction:

Central Nervous system sends message or impulse through efferent autonomic nerves. A message or impulse is nothing but the state of depolarization which is propagated through the nerve fibres for transmission of information through it. In normal resting state, a nerve cell is approximately −70 mV negative inside to the outside. This is resting membrane potential of a typical mammalian axon. At rest, the Na^+ concentration is high at extracellular space and low in intracellular fluid. Whereas the concentration of K^+ ion is nearly 40 fold higher in axoplasm than the extracellular fluid.

Though the K^+ ions can cross the resting axonal membrane, but Na^+ ions are not permeable through the membrane. These ionic gradients or the resting membrane potential is maintained by an energy dependent active transport or pump mechanism called the Na^+ K^+ ATPase or Na^+ K^+ pump which helps in efflux of 3 molecules of Na^+ and influx of 2 molecules of K^+ ions through the membrane.

Stimulation or arrival of an electrical impulse to a nerve fibre causes a sudden increase in Na^+ permeability. Na^+ enters into the fibre through Na^+ channels and thereby increases the positivity (depolarization) inside the fibre even up to + 20 mV (overshoot). K^+ ions then move out of the fibre in the direction of their concentration gradient to repolarize the area. Ionic distribution is normalized and the resting membrane potential is reestablished by the activation of Na^+K^+ pump. The events of Na^+ influx, depolarization, K^+ efflux, repolarization in a shorter form, is termed as action potential, An action potential, thus generated by a stimulus or arrival of an electrical impulse to a nerve fibre, steps up local circuit currents which activate voltage sensitive Na^+ channels at the next excitable part of the membrane and an impulse or action potential is propagated through a nerve fibre in this way.

Tetrodotoxin and saxitoxin selectively prevent the increase in permeability to Na^+ and thus block axonal conduction and produces flaccid type of paralysis. Batrachotoxin and scorpion toxins selectively increase Na^+ permeability to cause persistant depolarization which results in spastic paralysis. Local anaesthetics interfere with the Na^+ permeability and block axonal conduction.

Transmitters release:

Once an action potential arrives at the axonal terminal a number of sequential events take place. The depolarization of the area leads to stimulation and opening of the voltage sensitive Ca^+ channels of axonal membrane. Ca^+ enters into the axoplasm and helps in fusion

between the axoplasmic membrane and synaptic vesicles which are the store houses of neurotransmitters (excitatory or inhibitory), enzymes and some other proteins. The contents of those vesicles are then extruded out to the junctional cleft by a process called exocytosis. This neutrally mediated release can be modulated by the transmitter itself or by other agents through interaction with prejunctional membrane receptors. Norepinephrine (through α_2 adrenoceptors), dopamine, Acetylcholine (M_2), enkephalins and prostaglandins inhibit norepinephrine release. Whereas acetylcholine (N-receptors) and isoprenaline (β_2 receptor) accelerate the norepinephrine release.

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

The released transmitters rapidly migrate across the cleft and bind with specific receptors on the post junctional neuronal or effector cell membrane. The excitatory neurotransmitters bind with their receptors resulting in increase in Na^+ permeability which causes depolarization followed by K^+ efflux or repolarization. These changes are characterised as an "excitatory post-synaptic potential (EPSP)" which helps in either propagation of impulse through the post-ganglionic neurone or stimulation of effector organs (e.g., contraction of smooth muscles or secretion of glands).

Similarly, inhibitory neurotransmitters bind with their respective receptors to increase the permeability of K^+ and Cl^- which move in the direction of their concentration gradients (K^+ efflux and Cl^- influx) resulting in hyperpolarization (increased negativity inside the cell). These changes are termed as an "inhibitory post-synaptic potential (IPSP)" which stabilizes the post-synaptic membrane increasing the threshold to stimuli and elicits an inhibitory response in the cell.

During the resting state, small amount of neurotransmitter is released slowly but continuously from the nerve ending. Though the amount is not sufficient to elicit a response but produces electrical potential at the post-junctional membrane ("Miniature Endplate Potential", MEPP) that maintains the normal sensitivity of the effector organ to neurotransmitter.

The release transmitter combines with specific receptors on the postjunctional membrane and depending on its nature induces an excitatory postsynaptic potential (EPSP) or an inhibitory postsynaptic potential (IPSP).

EPSP: Increase in permeability to all cation – Na^+ or Ca^+ influx causes depolarization followed by K^+ efflux.

IPSP: Increase in permeability to smaller ions. That means K^+ and Cl^- moves in resulting in hyper polarization.

Destruction of the transmitter:

A maximum percentage of adrenergic neurotransmitter norepinephrine either re-enters into the presynaptic nerve terminal (uptake I) or diffuses away from the receptor sites (uptake

II). Rest amount is metabolized by both intra-neural (MAO) and extra-neural (COMT) enzymes. The released ACh is rapidly hydrolysed by acetyl-cholinesterase (AChE) enzyme that normally localizes in the synaptic cleft. Peptide neurotransmitters are hydrolysed by various peptidases and dissipated by diffusion; specific uptake mechanisms have not been demonstrated for these substance.

Co-transmission

In chemical synapse signals are transmitted across the synaptic cleft by means of chemical messenger (a neurotransmitter) released from the presynaptic axon terminal. Sometimes more than one neurotransmitter may be simultaneously released from axon. The additional neurotransmitter is called as a co-transmitter. These neurotransmitters have different receptors on the postsynaptic cell.

Examples:

(i) Noradrenaline, ATP in blood vessels, vas deferens.

(ii) Ach or GnRH in sympathetic ganglia.

(iii) Ach or Substance-P in enteric ganglia.

(iv) Ach or vasoactive intestinal peptide in salivary gland.

In the Autonomic nervous system besides the primary neurotransmitter (Acetylcholine and Noradrenaline), ATP, Adenosine peptides (vasoactive intestinal peptide, Neuropeptide, substance P, enkephalins) nitric oxide and prostaglandins as co-transmitter. In most autonomic cholinergic neurons **vasoactive intestinal peptide** (VIP) associated with acetylcholine, while ATP is associated with both acetylcholine and norepinephrine. The co-transmiter is stored in the same neuron but distinct synaptic vesicles or locations. However ATP is stored with norepinephrine (NE) in the same vesicle. On being released by the nerve impulse it may serve to regulate presynaptic release of the primary transmitter and/or postsynaptic sensitivity to it.

The role of adenosine 5'-triphosphate (ATP) as a major intracellular energy source is well-established. In addition, ATP and related nucleotides have widespread extracellular actions via the ionotropic P2X (ligand-gated cation channels) and metabotropic P2Y (G protein-coupled) receptors. When released from enteric nerves of the gastrointestinal tract it acts as an inhibitory neurotransmitter, mediating descending muscle relaxation during peristalsis. ATP is also an excitatory cotransmitter in autonomic nerves;

1. It is co-stored with noradrenaline in synaptic vesicles in postganglionic sympathetic nerves innervating smooth muscle preparations, such as the vas deferens and most arteries. When co-released with noradrenaline, ATP acts at post-junctional P2X1 receptors to evoke depolarisation, Ca^{2+} influx, Ca^{2+} sensitization and contraction.
2. ATP is also co-released with acetylcholine from post-ganglionic parasympathetic nerves innervating the urinary bladder and again acts at post-junctional P_2X_1 receptors, and possibly also a $P_2X_1 + 4$ heteromer, to elicit smooth muscle

contraction. In both cases the neurotransmitter actions of ATP are terminated by dephosphorylation by extracellular, membrane-bound enzymes and soluble nucleotidases released from post-ganglionic nerves.

8.3 CLASSIFICATION OF NEUROTRANSMITTER

Table 8.1: Classification of Neurotransmitter

Types of substance	Examples	Function
Ester	Acetylcholine	Excitory and Inhibitory
Amino acid	Glutamate, Aspartate	Excitory
	Glycine, GABA	Inhibitory
Amines (Catecholamine)	Epinephrine	Excitory and Inhibitory
	Norepinephrine	Excitory and Inhibitory
	Dopamine	Excitory and Inhibitory
Amines (Indolamine)	Serotonin	Excitory
	Histamine	Excitory
	Taurine	Inhibitory
Peptide	Endorphins	Excitory and Inhibitory
	Enkephalins	Excitory and Inhibitory
	Substance-P	Excitory and Inhibitory
	Cholecytokinin	Excitory and Inhibitory
Other	ATP, CO	Excitory
	Nitric oxide	Excitory and Inhibitory

Neurotransmitters are chemical messenger that transmit signal from neuron to the target cell (neuron, muscle cell gland) across a synapse. Neurotransmitters can be classified as either excitatory or inhibitory. Excitatory neurotransmitters function to activate receptors on the postsynaptic membrane and enhance the effects of the action potential, while inhibitory neurotransmitters function in a reverse mechanism. The following are the most clearly understood and most common types of neurotransmitters:

Acetylcholine: Acetylcholine is an excitatory neurotransmitter occurring throughout the nervous system and is the best understood and studied. It was the first neurotransmitter to be discovered and was isolated in 1921 by a German biologist named Otto Loewi, who later won a Nobel Prize for his work. Acetylcholine has many functions ranging from the stimulation of muscles, including the muscles of the gastrointestinal system to vital organs.

Norepinephrine: Norepinephrine, also known as noradrenaline, is an excitatory neurotransmitter secreted by the adrenal glands. It acts to increase the alertness of the nervous system as well as to stimulate the processes in the body. For example, it is very important in the endogenous production of epinephrine. It was first identified by a Swedish biologist called Ulf von Euler in 1946. Norepinephrine has been implicated in mood disorders such as anxiety, in which case its concentration in the body is abnormally high. Alternatively, an abnormally low concentration of it may lead to an impaired sleep cycle.

Epinephrine: Also known as adrenaline, epinephrine is an excitatory neurotransmitter produced by the adrenal glands and released into the bloodstream. It prepares the body for the fight or flight reaction. That means when a person is highly stimulated (fear, anger etc.), extra amounts of epinephrine are released into the bloodstream. This release of epinephrine increases the heart rate, the blood pressure and the glucose production from the liver (glycogenolysis). In this way, the nervous and the endocrine system prepare the body for dangerous and extreme situations.

Dopamine: Dopamine is considered a special type of neurotransmitter because its effects are both excitatory and inhibitory. It was discovered in the 1950s by another Swede, Arvid Carlsson. It is strongly associated with the reward mechanisms in the brain, and drugs such as cocaine, opium, heroin, and alcohol can temporarily increase its levels in the blood, leading to abnormal firing of nerve cells, which may sometimes manifest as intoxication, or several manners of consciousness/focus issues (such as not remembering where we put our keys, or forgetting what a paragraph said when we have just finished reading it, or simply day dreaming and not being able to stay on task). However, an appropriate secretion of dopamine in the bloodstream plays a role in the motivation or desire to complete a task.

GABA: Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter isolated in 1950 by Eugene Roberts and J. Awapara. An abnormally low secretion of GABA may cause conditions like anxiety. It is widely distributed in the brain and plays a principal role in reducing neuronal excitability throughout the nervous system.

Glutamate: Glutamate is another neurotransmitter with an excitatory effect and usually ensures homeostasis with the effects of GABA. It is the most common neurotransmitter in the central nervous system; however, excessive levels of it can be toxic to the nerve cells and may lead to conditions like stroke.

Serotonin: Serotonin is an inhibitory neurotransmitter that has been found to be intimately involved in emotion and mood. It was discovered by Vittorio Erspamer in the 1930s but was first found in blood serum in 1948 by Irvine Page who named it serotonin (meaning "serum-tonic"). Adequate amounts of serotonin are necessary for a stable mood, and also to balance any excessive excitatory neurotransmitter effects in the brain. Like norepinephrine, serotonin also regulates many processes in the body, such as carbohydrate cravings, the sleep cycle, pain control, and the digestion of food. An insufficient secretion of

serotonin may result in decreased immune system function, as well as a range of emotional disorders like depression, anger control problems, obsessive-compulsive disorder, and even suicidal tendencies.

Histamine: Histamine is an excitatory neurotransmitter produced by basophils and is found in high concentrations in the blood. It is involved primarily in the inflammatory responses, as well as a range of other functions such as vasodilation, and regulation of the immune response to foreign bodies. For example, when allergens are introduced into the bloodstream, histamine assists in the fight against these microorganisms causing itching of the skin or irritations of the throat, nose and/or lungs. It also plays a role in the wake/sleep cycle, by increasing wakefulness.

QUESTIONS

1. Define neurotransmitter.
2. Define co-transmission.
3. Classify neurotransmitter with suitable example.
4. Write the various steps of neurohumoral transmission.

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