■ DEFINITION

Synapse is the junction between two neurons. It is not an anatomical continuation. But, it is only a physiological continuity between two nerve cells.

■ CLASSIFICATION OF SYNAPSE

Synapse is classified by two methods:

A. Anatomical classification
B. Functional classification.

■ ANATOMICAL CLASSIFICATION

Usually synapse is formed by axon of one neuron ending on the cell body, dendrite or axon of the next neuron. Depending upon **ending of axon,** synapse is classified into three types:

1. **Axoaxonic synapse** in which axon of one neuron terminates on axon of another neuron
2. **Axodendritic synapse** in which the axon of one neuron terminates on dendrite of another neuron
3. **Axosomatic synapse** in which axon of one neuron ends on soma (cell body) of another neuron (Fig. 140.1).

■ FUNCTIONAL CLASSIFICATION

Functional classification of synapse is on the basis of **mode of impulse transmission.** According to this, synapse is classified into two categories:

1. Electrical synapse
2. Chemical synapse.

However, generally the word synapse refers to a chemical synapse.

1. *Electrical Synapse*

Electrical synapse is the synapse in which the physiological continuity between the presynaptic and the post-

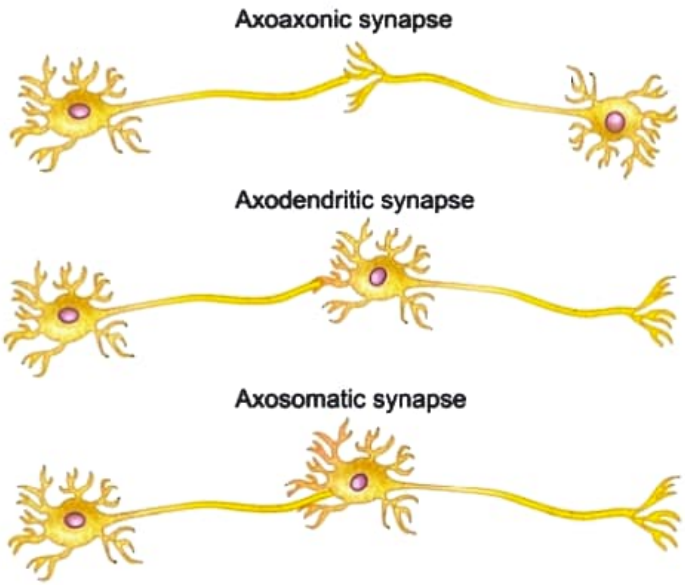

FIGURE 140.1: Anatomical synapses

synaptic neurons is provided by **gap junction** between the two neurons (Fig. 140.2). There is **direct exchange** of ions between the two neurons through the gap junction. Because of this reason, the action potential reaching the terminal portion of presynaptic neuron directly enters the postsynaptic neuron.

Important feature of electrical synapse is that the synaptic delay is very less because of the direct flow of current. Moreover, the impulse is transmitted in either direction through the electrical synapse.

This type of impulse transmission occurs in some tissues like the cardiac muscle fibers, smooth muscle fibers of intestine and the epithelial cells of lens in the eye.

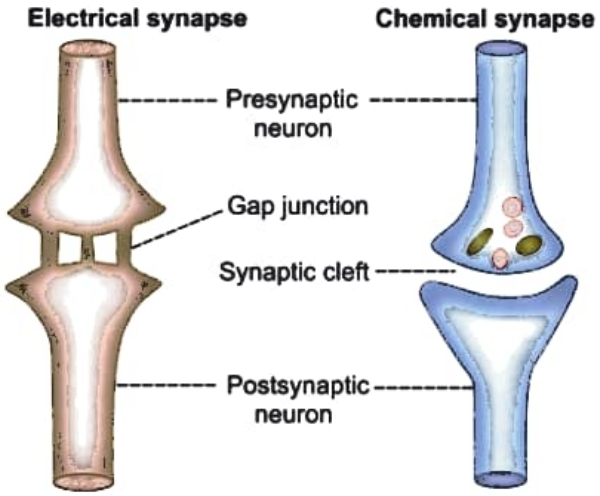

FIGURE 140.2: Electrical and chemical synapse

2. Chemical Synapse

Chemical synapse is the junction between a nerve fiber and a muscle fiber or between two nerve fibers, through which the signals are transmitted by the release of chemical transmitter. In the chemical synapse, there is no continuity between the two neurons because of the presence of a space called **synaptic cleft** between the two neurons. Action potential reaching the presynaptic terminal causes release of neurotransmitter substance from the vesicles of this terminal. Neurotransmitter reaches the postsynaptic neuron through synaptic cleft and causes the production of potential change. Structure and functions of the chemical synapse are given here.

■ FUNCTIONAL ANATOMY OF CHEMICAL SYNAPSE

Functional anatomy of a chemical synapse is shown in Figure 140.3. Neuron from which the axon arises is called the **presynaptic neuron** and the neuron on which the axon ends is called **postsynaptic neuron.** Axon of the presynaptic neuron divides into many small branches before forming the synapse. These branches are known as presynaptic **axon terminals.**

Types of Axon Terminals

1. *Terminal knobs*

Some of the terminals are enlarged slightly like knobs called **terminal knobs.** Terminal knobs are concerned with excitatory function of the synapse.

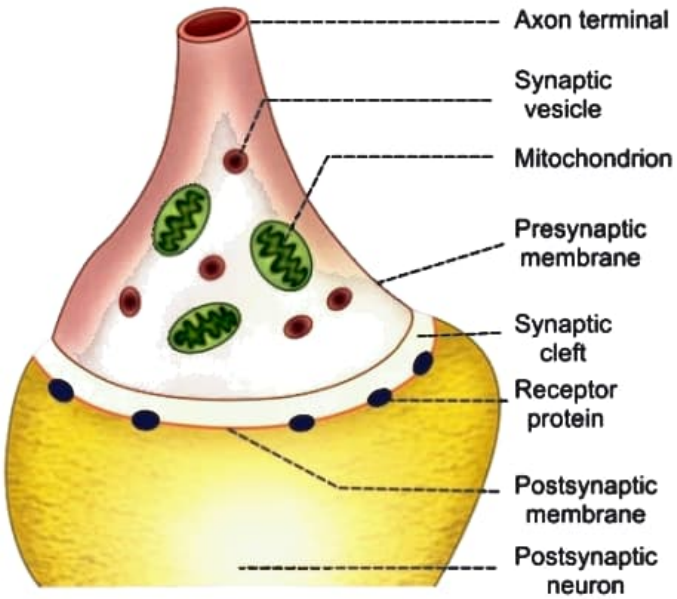

FIGURE 140.3: Structure of chemical synapse

2. *Terminal coils or free endings*

Other terminals are wavy or coiled with free ending without the knob. These terminals are concerned with inhibitory function.

Structures of Axon Terminals and Presynaptic Membrane

Presynaptic axon terminal has a definite intact membrane known as **presynaptic membrane.**

Axon terminal has two important structures:

i. **Mitochondria,** which help in the synthesis of neurotransmitter substance
ii. **Synaptic vesicles,** which store neurotransmitter substance.

Synaptic Cleft and Postsynaptic Membrane

Membrane of the postsynaptic neuron is called **postsynaptic membrane.** It contains some **receptor proteins.** Small space in between the presynaptic membrane and the postsynaptic membrane is called **synaptic cleft.** The **basal lamina** of this cleft contains **cholinesterase,** which destroys **acetylcholine.**

■ FUNCTIONS OF SYNAPSE

Main function of the synapse is to transmit the impulses, i.e. action potential from one neuron to another. However, some of the synapses inhibit these impulses. So the impulses are not transmitted to the postsynaptic neuron.

On the basis of functions, synapses are divided into two types:

1. Excitatory synapses, which transmit the impulses (excitatory function)
2. Inhibitory synapses, which inhibit the transmission of impulses (inhibitory function).

■ EXCITATORY FUNCTION

Excitatory Postsynaptic Potential

Excitatory postsynaptic potential (EPSP) is the non-propagated electrical potential that develops during the process of synaptic transmission. When the action potential reaches the presynaptic axon terminal, the voltage-gated **calcium channels** at the presynaptic membrane are opened. Now, the **calcium ions** enter the axon terminal from ECF (Fig. 140.4).

Calcium ions cause the release of neurotransmitter substance from the vesicles by means of **exocytosis.**

Neurotransmitter, which is excitatory in function (excitatory neurotransmitter) passes through presynaptic membrane and synaptic cleft and reaches the postsynaptic membrane. Now, the neurotransmitter binds with receptor protein present in postsynaptic membrane to form neurotransmitter-receptor complex. Neurotransmitter-receptor complex causes production of a non-propagated EPSP. Common excitatory neurotransmitter in a synapse is **acetylcholine.**

Mechanism of Development of EPSP

Neurotransmitter-receptor complex causes opening of ligand-gated **sodium channels.** Now, the **sodium ions**

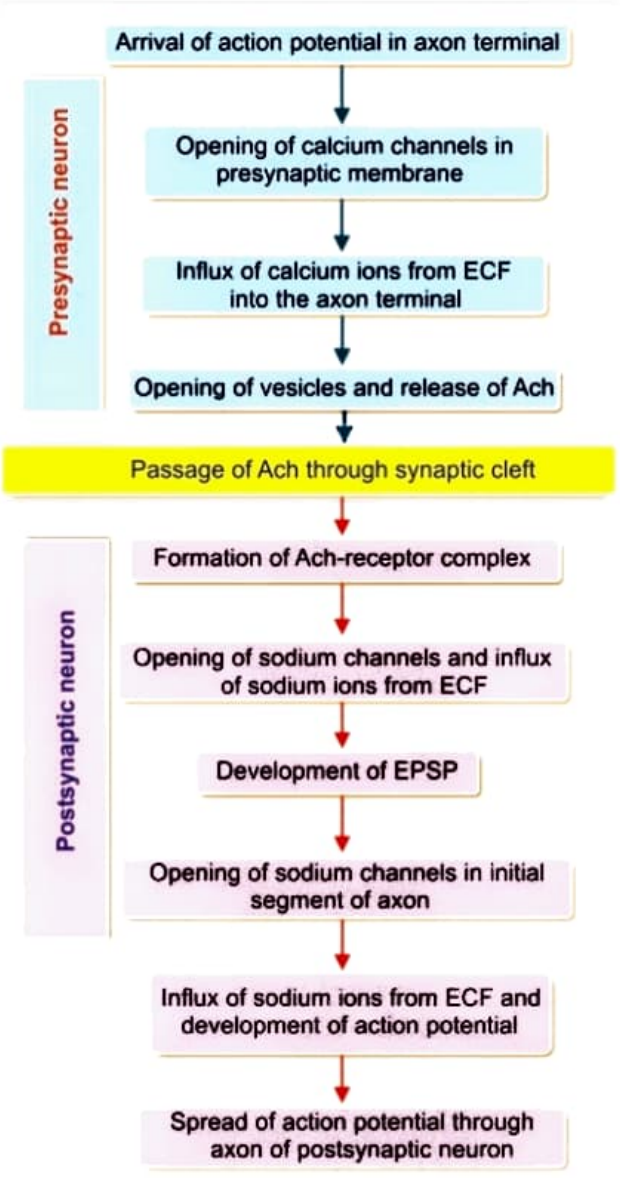

FIGURE 140.4: Sequence of events during synaptic transmission. Ach = Acetylcholine, ECF = Extracellular fluid, EPSP = Excitatory postsynaptic potential.

from ECF enter the cell body of postsynaptic neuron. As the sodium ions are positively charged, resting membrane potential inside the cell body is altered and **mild depolarization** develops. This type of mild depolarization is called EPSP. It is a **local potential** (response) in the synapse.

Properties of EPSP

EPSP is confined only to the synapse. It is a **graded potential** (Chapter 31). It is similar to receptor potential and endplate potential.

EPSP has two properties:

1. It is non-propagated
2. It does not obey all-or-none law.

Significance of EPSP

EPSP is not transmitted into the axon of postsynaptic neuron. However, it causes development of action potential in the axon.

When EPSP is strong enough, it causes the opening of voltage-gated **sodium channels** in the initial segment of axon. Now, due to the entrance of **sodium ions,** the depolarization occurs in the initial segment of axon and thus, the action potential develops. From here, the action potential spreads to other segment of the axon.

■ INHIBITORY FUNCTION

Inhibition of synaptic transmission is classified into five types:

1. Postsynaptic or direct inhibition
2. Presynaptic or indirect inhibition
3. Negative feedback or Renshaw cell inhibition
4. Feedforward inhibition
5. Reciprocal inhibition.

1. *Postsynaptic or Direct Inhibition*

Postsynaptic inhibition is the type of synaptic inhibition that occurs due to the release of an inhibitory neurotransmitter from presynaptic terminal instead of an excitatory neurotransmitter substance. It is also called **direct inhibition.** Inhibitory neurotransmitters are gamma-aminobutyric acid **(GABA),** dopamine and glycine.

Action of GABA – development of inhibitory postsynaptic potential

Inhibitory postsynaptic potential (IPSP) is the electrical potential in the form of **hyperpolarization** that develops during postsynaptic inhibition. Inhibitory neurotransmitter substance acts on postsynaptic membrane by binding with receptor. Transmitter-receptor complex opens the ligand-gated **potassium channels** instead of sodium channels. Now, the **potassium ions,** which are available in plenty in the cell body of postsynaptic neuron move to ECF. Simultaneously, **chloride channels** also open and chloride ions (which are more in ECF) move inside the cell body of postsynaptic neuron. The exit of potassium ions and influx of chloride ions cause **more negativity** inside, leading to **hyperpolarization.** Hyperpolarized state of the synapse inhibits synaptic transmission (Fig. 140.5).

2. *Presynaptic or Indirect Inhibition*

Presynaptic inhibition occurs due to the failure of presynaptic axon terminal to release sufficient quantity of excitatory neurotransmitter substance. It is also called indirect inhibition.

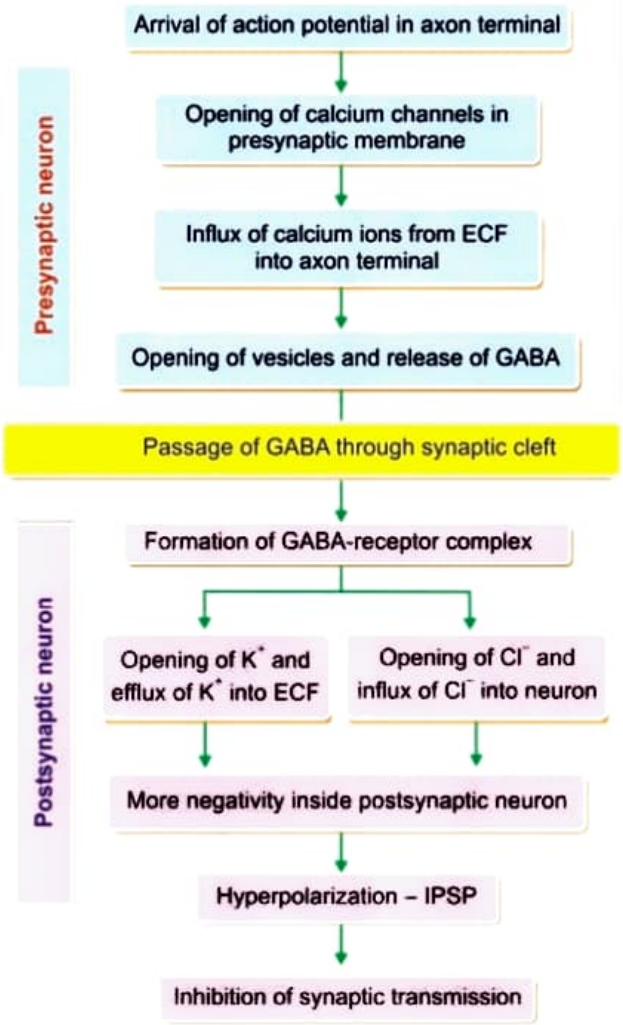

FIGURE 140.5: Sequence of events during postsynaptic inhibition. GABA = Gamma-aminobutyric acid, ECF = Extracellular fluid, IPSP = Inhibitory postsynaptic potential.

Presynaptic inhibition is mediated by axoaxonal synapses. It is prominent in **spinal cord** and regulates the propagation of information to higher centers in brain.

Normally, during synaptic transmission, action potential reaching the presynaptic neuron produces development of EPSP in the postsynaptic neuron. But, in spinal cord, a **modulatory neuron** called **presynaptic inhibitory neuron** forms an axoaxonic synapse with the presynaptic neuron (Fig. 140.6).

This inhibitory neuron inhibits the presynaptic neuron and decreases the magnitude of action potential in presynaptic neuron. The **smaller action potential** reduces **calcium influx.** This in turn decreases the quantity of neurotransmitter released by presynaptic neuron. So the magnitude of EPSP in postsynaptic neuron is decreased resulting in synaptic inhibition.

3. *Renshaw Cell or Negative Feedback Inhibition*

Negative feedback inhibition is the type of synaptic inhibition, which is caused by Renshaw cells in **spinal cord.** Renshaw cells are small motor neurons present in anterior gray horn of spinal cord (Chapter 143). Anterior nerve root consists of nerve fibers, which leave the spinal cord. These nerve fibers arise from α-motor neurons in anterior gray horn of the spinal cord and reach the effector organ, muscles. Some of the fibers called collaterals fibers terminate on Renshaw cells instead of leaving the spinal cord.

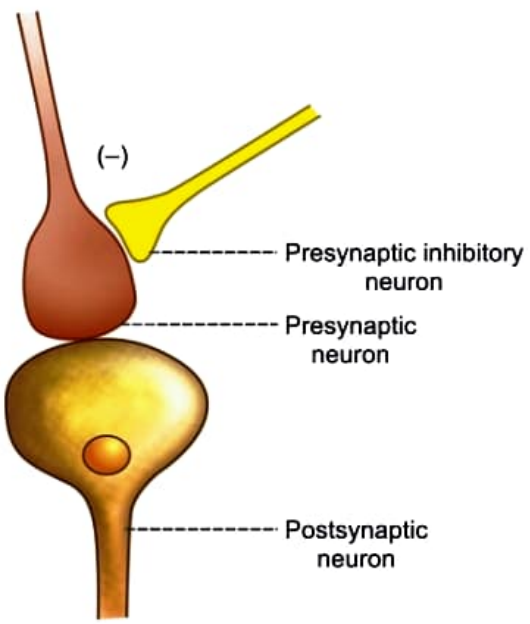

FIGURE 140.6: Presynaptic inhibition

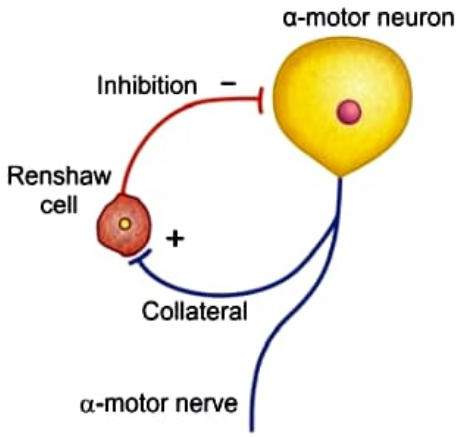

FIGURE 140.7: Renshaw cell inhibition

When motor neurons send motor impulses, some of the impulses reach the Renshaw cell by passing through **collaterals.** Now, the Renshaw cell is stimulated. In turn, it sends inhibitory impulses to α-motor neurons so that, the discharge from motor neurons is reduced (Fig. 140.7).

In this way, Renshaw cell inhibition represents a **negative feedback mechanism.** A Renshaw cell may be supplied by more than one alpha motor neuron collateral and it may synapse on many motor neurons.

4. *Feedforward Inhibition*

Feedforward synaptic inhibition occurs in **cerebellum** and it controls the **neuronal activity** in cerebellum.

During the process of neuronal activity in cerebellum, stellate cells and basket cells, which are activated by granule cells, inhibit the **Purkinje cells** by releasing **GABA** (Chapter 150). This type of inhibition is called feedforward inhibition.

5. *Reciprocal Inhibition*

Inhibition of antagonistic muscles when a group of muscles are activated is called reciprocal inhibition. It is because of **reciprocal innervation** (Chapter 142).

Significance of Synaptic Inhibition

Synaptic inhibition in CNS limits the number of impulses going to muscles and enables the muscles to act properly and appropriately. Thus, the inhibition helps to select exact number of impulses and to omit or block the excess ones. When a poison like **strychnine** is introduced into the body, it destroys the inhibitory

function at synaptic level resulting in continuous and convulsive contraction even with slight stimulation. In the nervous disorders like **parkinsonism,** the inhibitory system is impaired resulting in rigidity.

■ PROPERTIES OF SYNAPSE

■ 1. ONE WAY CONDUCTION – BELL-MAGENDIE LAW

According to Bell-Magendie law, the impulses are transmitted only in **one direction** in synapse, i.e. from presynaptic neuron to postsynaptic neuron.

■ 2. SYNAPTIC DELAY

Synaptic delay is a short delay that occurs during the transmission of impulses through the synapse. It is due to the time taken for:

i. Release of neurotransmitter
ii. Passage of neurotransmitter from axon terminal to postsynaptic membrane
iii. Action of the neurotransmitter to open the ionic channels in postsynaptic membrane.

Normal duration of synaptic delay is 0.3 to 0.5 millisecond. Synaptic delay is one of the causes for **reaction time** of reflex activity.

Significance of Determining Synaptic Delay

Determination of synaptic delay helps to find out whether the pathway for a reflex is monosynapatic or polysynaptic.

■ 3. FATIGUE

During continuous muscular activity, synapse becomes the seat of fatigue along with **Betz cells** present in motor area of frontal lobe of cerebral cortex (Refer Chapter 30 for details of fatigue). Fatigue at synapse is due to the **depletion of neurotransmitter** substance, acetylcholine.

Depletion of acetylcholine occurs because of two factors:

i. Soon after the action, acetylcholine is destroyed by acetylcholinesterase
ii. Due to continuous action, new acetylcholine is not synthesized.

■ 4. SUMMATION

Summation is the fusion of effects or progressive increase in the excitatory postsynaptic potential in postsynaptic neuron when many presynaptic excitatory terminals are stimulated simultaneously or when single presynaptic terminal is stimulated repeatedly. Increased EPSP triggers the axon potential in the initial segment of axon of postsynaptic neuron (Fig.140.8).

Summation is of two types:

i. *Spatial Summation*

Spatial summation occurs when many presynaptic terminals are stimulated simultaneously.

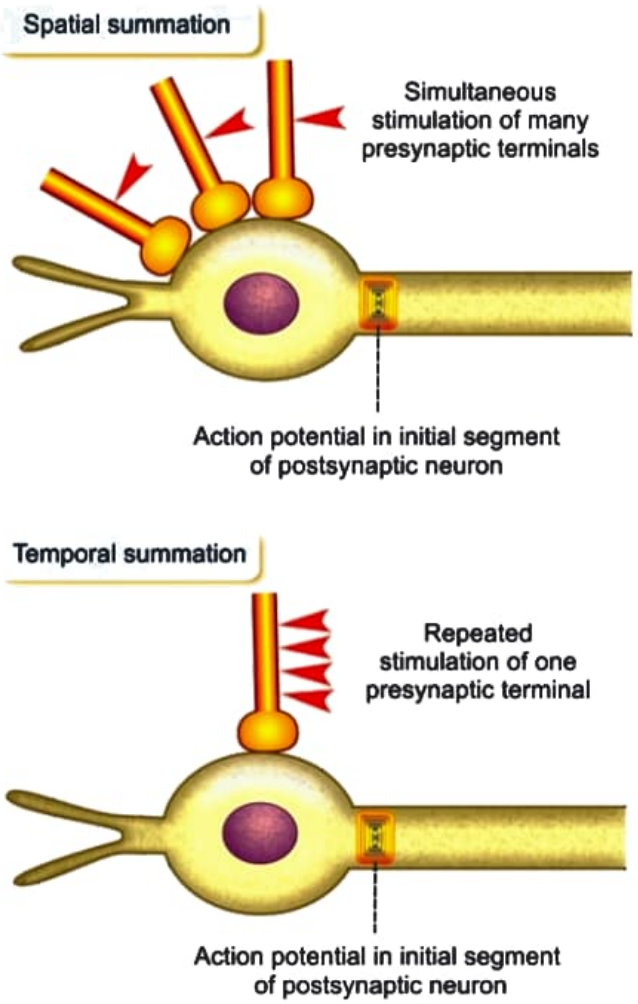

FIGURE 140.8: Spatial and temporal summation

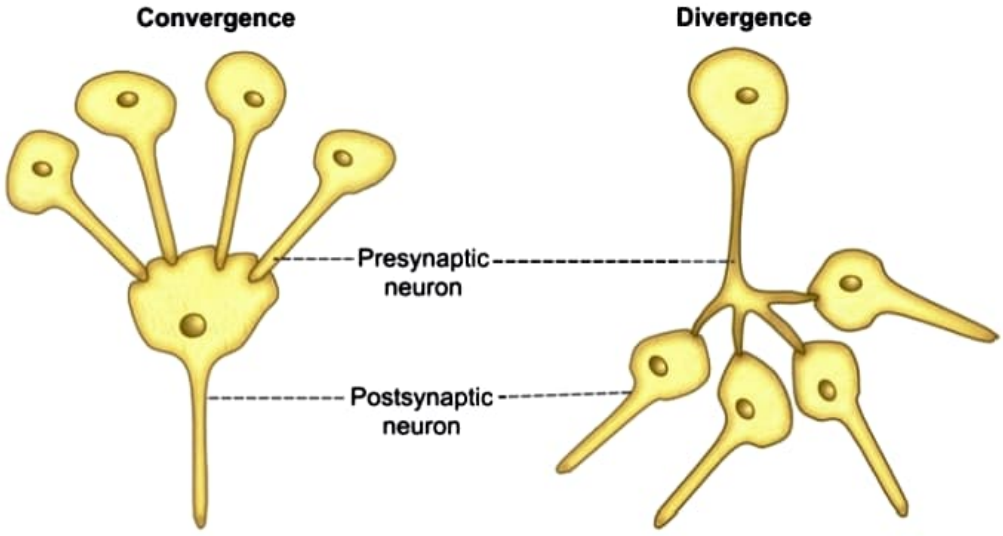

FIGURE 140.9: Convergence and divergence

ii. *Temporal Summation*

Temporal summation occurs when one presynaptic terminal is stimulated repeatedly.

Thus, both spatial summation and temporal summation play an important role in facilitation of response.

■ 5. ELECTRICAL PROPERTY

Electrical properties of the synapse are the EPSP and IPSP, which are already described in this chapter.

■ CONVERGENCE AND DIVERGENCE

■ CONVERGENCE

Convergence is the process by which many presynaptic neurons terminate on a single postsynaptic neuron (Fig.140.9).

■ DIVERGENCE

Divergence is the process by which one presynaptic neuron terminates on many postsynaptic neurons.

Neurotransmitters

■ DEFINITION

Neurotransmitter is a chemical substance that acts as a **mediator** for the transmission of nerve impulse from one neuron to another neuron through a synapse.

■ HISTORY

Existence of neurotransmitter was first discovered by an Austrian scientist named **Otto Loewi** in 1921. He dreamt of an experiment, which he did practically and came out with this discovery.

Loewi Experiment

Otto Loewi used two frogs for this experiment. Heart of frog A was with intact vagus nerve and was placed in a saline-filled chamber. Heart of frog B was denervated and was kept in another saline-filled chamber. Both the chambers were connected in such a way that the fluid from chamber of frog A could flow into the chamber of frog B.

When vagus nerve of frog A was electrically stimulated, slowing of heart rate was observed. After a short delay, the heart rate in frog B also was found to be slowing down. From this observation, Loewi speculated that some chemical substance must have been released from the vagus nerve of frog A, which was responsible for the slowing down of the heart rate in frog B. He named it as **'vagusstoff'**. Later this chemical substance was considered as a neurotransmitter and called acetylcholine (Ach).

■ CRITERIA FOR NEUROTRANSMITTER

Nowadays, many substances are categorized as neurotransmitters. To consider a substance as a neurotransmitter, it should fulfill certain criteria as given below:

1. It must be found in a neuron
2. It must be produced by a neuron
3. It must be released by a neuron
4. After release, it must act on a target area and produce some biological effect
5. After the action, it must be inactivated.

■ CLASSIFICATION OF NEUROTRANSMITTERS

■ DEPENDING UPON CHEMICAL NATURE

Many substances of different chemical nature are identified as neurotransmitters. Depending upon their

chemical nature, neurotransmitters are classified into three groups.

1. *Amino Acids*

Neurotransmitters of this group are involved in **fast synaptic transmission** and are inhibitory and excitatory in action. GABA, glycine, glutamate (glutamic acid) and aspartate (aspartic acid) belong to this group.

2. *Amines*

Amines are the modified amino acids. These neurotransmitters involve in **slow synaptic transmission.** These neurotransmitters are also inhibitory and excitatory in action. Noradrenaline, adrenaline, dopamine, serotonin and histamine belong to this group.

3. *Others*

Some neurotransmitters do not fit into any of these categories. One such substance is acetylcholine. It is formed from the choline and acetyl coenzyme A in the presence of the enzyme called choline acetyltransferase. Another substance included in this category is the soluble gas nitric oxide (NO).

■ DEPENDING UPON FUNCTION

Some of the neurotransmitters cause excitation of postsynaptic neuron while others cause inhibition.

Thus, neurotransmitters are classified into two types:

1. Excitatory neurotransmitters
2. Inhibitory neurotransmitters.

1. *Excitatory Neurotransmitters*

Excitatory neurotransmitter is a chemical substance, which is responsible for the conduction of impulse from presynaptic neuron to postsynaptic neuron. Neurotransmitter released from the presynaptic axon terminal does not cause development of action potential in the postsynaptic neuron. Rather, it causes some change in the resting membrane potential, i.e. slight depolarization by the opening of sodium channels in the postsynaptic membrane and the influx of sodium ions from ECF. This slight depolarization is called **excitatory postsynaptic potential (EPSP).** EPSP in turn causes development of action potential in the initial segment of the axon of the postsynaptic neuron (Chapter 140).

TABLE 141.1: Neurotransmitters

Group	Name	Site of secretion	Action
Aminoacids	GABA	Cerebral cortex, cerebellum, basal ganglia, retina and spinal cord	Inhibitory
	Glycine	Forebrain, brainstem, spinal cord and retina	Inhibitory
	Glutamate	Cerebral cortex, brainstem and cerebellum	Excitatory
	Aspartate	Cerebellum, spinal cord and retina	Excitatory
Amines	Noradrenaline	Postganglionic adrenergic sympathetic nerve endings, cerebral cortex, hypothalamus, basal ganglia, brainstem, locus coeruleus and spinal cord	Excitatory and inhibitory
	Adrenaline	Hypothalamus, thalamus and spinal cord	Excitatory and inhibitory
	Dopamine	Basal ganglia, hypothalamus, limbic system, neocortex, retina and sympathetic ganglia	Inhibitory
	Serotonin	Hypothalamus, limbic system, cerebellum, spinal cord, retina, gastrointestinal (GI) tract, lungs and platelets	Inhibitory
	Histamine	Hypothalamus, cerebral cortex, GI tract and mast cells	Excitatory
Others	Nitric oxide	Many parts of CNS, neuromuscular junction and GI tract	Excitatory
	Acetylcholine	Preganglionic parasympathetic nerve endings Postganglionic parasympathetic nerve endings Preganglionic sympathetic nerve endings Postganglionic sympathetic cholinergic nerve endings Neuromuscular junction, cerebral cortex, hypothalamus, basal ganglia, thalamus, hippocampus and amacrine cells of retina	Excitatory

GABA = Gamma-aminobutyric acid, CNS = Central nervous system.

Common excitatory neurotransmitters are **acetylcholine** and **noradrenaline.**

2. *Inhibitory Neurotransmitters*

Inhibitory neurotransmitter is a chemical substance, which inhibits the conduction of impulse from the presynaptic neuron to the postsynaptic neuron (Chapter 140). When it is released from the presynaptic axon terminal due to the arrival of action potential, it causes opening of potassium channels in the postsynaptic membrane and efflux of potassium ions. This leads to hyperpolarization, which is called the **inhibitory postsynaptic potential (IPSP).** When IPSP is developed, the action potential is not generated in the postsynaptic neuron.

Common inhibitory neurotransmitters are **gamma-aminobutyric acid (GABA)** and dopamine.

■ TRANSPORT AND RELEASE OF NEUROTRANSMITTER

Neurotransmitter is produced in the cell body of the neuron and is transported through axon. At the axon terminal, the neurotransmitter is stored in small packets called vesicles. Under the influence of a stimulus, these vesicles open and release the neurotransmitter into synaptic cleft. It binds to specific receptors on the surface of the postsynaptic cell. Receptors are G proteins, protein kinase or ligand-gated receptors.

■ INACTIVATION OF NEUROTRANSMITTER

After the execution of the action, neurotransmitter is inactivated by four different mechanisms:

1. It diffuses out of synaptic cleft to the area where it has no action
2. It is destroyed or disintegrated by specific enzymes
3. It is engulfed and removed by astrocytes (macrophages)
4. It is removed by means of reuptake into the axon terminal.

■ REUPTAKE OF NEUROTRANSMITTER

Reuptake is a process by which the neurotransmitter is taken back from synaptic cleft into the axon terminal after execution of its action. Reuptake process involves a specific carrier protein for each neurotransmitter.

■ IMPORTANT NEUROTRANSMITTERS

Some of the important neurotransmitters are described here. Details of neurotransmitters are given in Tables 141.1 and 141.2.

■ ACETYLCHOLINE

Acetylcholine is a **cholinergic neurotransmitter.** It possesses excitatory function. It produces the excitatory function by opening the ligand-gated sodium channels (Chapters 32 and 140).

Source

Acetylcholine is the transmitter substance at the neuromuscular junction and synapse. It is also released by the following nerve endings:

1. Preganglionic parasympathetic nerve
2. Postganglionic parasympathetic nerve
3. Preganglionic sympathetic nerve
4. Postganglionic sympathetic cholinergic nerves:
   i. Nerves supplying eccrine sweat glands
   ii. Sympathetic vasodilator nerves in skeletal muscle
5. Nerves in amacrine cells of retina
6. Many regions of brain.

Synthesis

Ach is synthesized in the cholinergic nerve endings. Synthesis takes place in axoplasm and Ach is stored in the vesicles. It is synthesized from acetyl coenzyme A (acetyl CoA). It combines with choline in the presence of the enzyme choline acetyltransferase to form Ach.

TABLE 141.2: Excitatory and inhibitory neurotransmitters

Excitatory neurotransmitters	Inhibitory neurotransmitters	Neurotransmitters with excitatory and inhibitory actions
1. Acetylcholine	1. Gamma-aminobutyric acid	1. Noradrenaline
2. Nitric oxide	2. Glycine	2. Adrenaline
3. Histamine	3. Dopamine	
4. Glutamate	4. Serotonin	
5. Aspartate		

Fate

Action of Ach is short lived. Within one millisecond after the release from the vesicles, it is hydrolyzed into acetate and choline by the enzyme **acetylcholinesterase** (Fig. 141.1). This enzyme is present in basal lamina of the synaptic cleft.

Acetylcholine Receptors

There are two types of receptors through which Ach acts on the tissues namely, **muscarinic receptors** and **nicotinic receptors**. Reason for the terminology of these receptors is as follows: Poisonous substance from toadstools called **muscarine,** acts on a specific group of receptors known as muscarinic receptors; similarly, another substance called **nicotine** acts on a specific group of receptors known as nicotinic receptors but Ach acts on both the receptors.

Muscarinic receptors are present in all the organs innervated by the postganglionic fibers of the parasympathetic system and by the sympathetic cholinergic nerves. Nicotinic receptors are present in the synapses between preganglionic and postganglionic neurons of both sympathetic and parasympathetic systems.

Nicotinic receptors are also present in the neuromuscular junction on membrane of skeletal muscle.

■ NORADRENALINE

Noradrenaline is the neurotransmitter in adrenergic nerve fibers. It is released from the following structures:

1. Postganglionic sympathetic nerve endings
2. Cerebral cortex

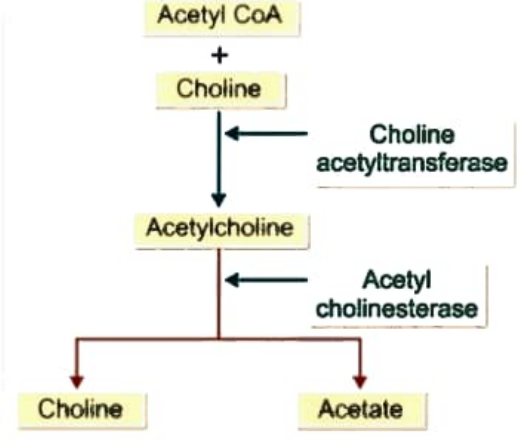

FIGURE 141.1: Synthesis and breakdown of acetylcholine

3. Hypothalamus
4. Basal ganglia
5. Brainstem
6. Locus ceruleus in pons
7. Spinal cord.

In many places, noradrenaline is the **excitatory** chemical mediator and in very few places, it causes **inhibition.** It is believed to be involved in dreams, arousal and elevation of moods. Refer Chapter 71 for the synthesis of noradrenaline.

■ DOPAMINE

Dopamine is secreted by nerve endings in the following areas:

1. Basal ganglia
2. Hypothalamus
3. Limbic system
4. Neocortex
5. Retina
6. Small, intensely fluorescent cells in sympathetic ganglia.

Dopamine possesses **inhibitory** action. Prolactin inhibitory hormone secreted by hypothalamus is considered to be dopamine. Refer Chapter 71 for the synthesis of dopamine.

■ SEROTONIN

Serotonin is otherwise known as **5-hydroxytryptamine** (5-HT). It is synthesized from tryptophan by hydroxylation and decarboxylation. Large amount of serotonin (90%) is found in enterochromatin cells of GI tract. Small amount is found in platelets and nervous system. It is secreted in the following structures:

1. Hypothalamus
2. Limbic system
3. Cerebellum
4. Dorsal raphe nucleus of midbrain
5. Spinal cord
6. Retina
7. GI tract
8. Lungs
9. Platelets.

It is an **inhibitory** substance. It inhibits impulses of pain sensation in posterior gray horn of spinal cord. It is supposed to cause depression of mood and sleep (Chapter 145). Serotonin causes vasoconstriction, platelet aggregation and smooth muscle contraction. It also controls food intake.

■ HISTAMINE

Histamine is secreted in nerve endings of hypothalamus, limbic cortex and other parts of cerebral cortex. It is also secreted by gastric mucosa and mast cells. Histamine is an **excitatory** neurotransmitter. It is believed to play an important role in arousal mechanism.

■ GAMMA-AMINOBUTYRIC ACID

Gamma-aminobutyric acid (GABA) is an **inhibitory** neurotransmitter in synapses particularly in CNS. It is responsible for presynaptic inhibition. It is secreted by nerve endings in the following structures:

1. Cerebral cortex
2. Cerebellum
3. Basal ganglia
4. Spinal cord
5. Retina.

GABA causes synaptic inhibition by opening potassium channels and chloride channels. So, potassium comes out of synapse and chloride enters in (Chapter 140). This leads to hyperpolarization, which is known as inhibitory postsynaptic potential (IPSP).

■ SUBSTANCE P

Substance P is a neuropeptide that acts as a neurotransmitter and as a neuromodulator (see below). Substance P is a polypeptide with 11 amino acid residues. It belongs to a family of 3 related peptides called **neurokinins** or **tachykinins.** The other peptides of this family are neurokinin A and neurokinin B which are not well known like substance P.

Substance P is secreted by the nerve endings (first order neurons) of pain pathway in spinal cord. It is also found in many peripheral nerves, different parts of brain particularly hypothalamus, retina and intestine (Chapter 44).

It mediates **pain sensation.** It is a potent vasodilator in CNS. It is responsible for regulation of anxiety, stress, mood disorders, neurotoxicity, nausea and vomiting.

■ NITRIC OXIDE

Nitric oxide (NO) is a neurotransmitter in the CNS. It is also the important neurotransmitter in the neuromuscular junctions between the inhibitory motor fibers of intrinsic nerve plexus and the smooth muscle fibers of GI tract.

Nitric oxide acts as a mediator for the **dilator effect** of Ach on small arteries. In the smooth muscle fibers of arterioles, NO activates the enzyme guanylyl cyclase, which in turn causes formation of cyclic guanosine monophosphate (cGMP) from GMP. The cGMP is a smooth muscle relaxant and it causes dilatation of arterioles. Thus, NO indirectly causes dilatation of arterioles.

Peculiarity of NO is that it is neither produced by the neuronal cells nor stored in the vesicles. It is produced by **non-neuronal cells** like the endothelial cells of blood vessels. From the site of production, it diffuses into the neuronal and non-neuronal cells where it exerts its action.

■ NEUROMODULATORS

Definition

Neuromodulator is the chemical messenger, which modifies and regulates activities that take place during the synaptic transmission.

These peptides do not propagate nerve impulses like neurotransmitters.

Neuromodulators Vs Neurotransmitters

Neuromodulators are distinct from neurotransmitters. However, both the terms are wrongly interchanged. Neurotransmitters propagate nerve impulses through synapse whereas neuromodulators modify and regulate the activities of synaptic transmission (Table 141.3).

Neurotransmitters are packed in small vesicles in axon terminals only. But neuromodulators are generally

TABLE 141.3: Differences between neurotransmitters and neuromodulators

Sl No	Neurotransmitters	Neuromodulators
1	Propagate nerve impulse through synapse	Modify and regulate synaptic transmission
2	Packed in small synaptic vesicles	Packed in large synaptic vesicles
3	Found only in axon terminals	Found in all parts of the body
4	Generally, neuron has only one neurotransmitter	Neuron may have one or more neuromodulators
5	Act by changing the electric potential – depolarization or repolarization	Have diverse actions
6	Chemically, neurotransmitters are amino acids, amine or others	Chemically, neuromodulators are only peptides

packed in large synaptic vesicles, which are present in all parts of neuron like soma, dendrite, axon and nerve endings. Many neurons have one conventional neurotransmitter and one or more neuromodulators.

Few peptides like substance P (see above) act as neurotransmitters and neuromodulators.

Actions of Neuromodulators

Neurotransmitters affect the excitability of other neurons or other tissues (like muscle fiber) by producing **depolarization** or **hyperpolarization** through the receptors of ionic channels. But neuromodulators have diverse actions such as:

1. Regulation of synthesis, breakdown or reuptake of neurotransmitter
2. Excitation or inhibition of membrane receptors by acting independently or together with neurotransmitter
3. Control of gene expression
4. Regulation of local blood flow
5. Promotion of synaptic formation
6. Control of glial cell morphology
7. Regulation of behavior.

Chemistry of Neuromodulators

Generally the neuromodulators are **peptides**. So neuromodulators are often referred as **neuropeptides.** Almost all the peptides found in nervous tissues are neuromodulators.

Types of Neuromodulators

Neuromodulators are classified into two types:

1. Non-opioid peptides
2. Opioid peptides.

■ NON-OPIOID PEPTIDES

Non-opioid neuropeptides act by binding with G-protein coupled receptors. These neuropeptides are also called **non-opioid neuromodulators.** Non-opioid peptides are listed in Table 141.4.

■ OPIOID PEPTIDES

Peptides, which bind to opioid receptors are called **opioid peptides** (Table 141.5). Opioid peptides are also called opioid neuropeptides or opioid neuromodulators. Opioid receptors are the membrane proteins located in nerve endings in brain and GI tract. Opioid receptors are of three types μ, κ and δ. These proteins are called **opioid receptors** because of their affinity towards the opiate or morphine, which are derived from opium.

Opium is the juice of white **poppy** ***(Papaver somniferum).*** It is used as a narcotic to produce hallucinations and induce sleep. Opiate also induces sleep. **Morphine** is a powerful analgesic (pain reliever). Both opiate and morphine have high medicinal values, but are highly addictive.

These two substances act by binding with the receptor proteins (opioid receptors) for the natural neuropeptides. Natural neuropeptides are called **endogenous opioid peptides.**

Endogenous opioid peptides have opiate like activity and inhibit the neurons in the brain involved in pain sensation.

Opioid peptides are of three types:

i. Enkephalins
ii. Dynorphins
iii. Endorphins.

i. *Enkephalins*

Enkephalins are the natural opiate peptides recognized first in pig's brain. Derived from the precursor proenkephalin, these peptides are present in the nerve endings in many parts of forebrain, substantia gelatinosa of brainstem, spinal cord and GI tract. Two types of enkephalins are known, **leucine** enkephalin (YGGFL) and **methionine** enkephalin (YGGFM).

ii. *Dynorphins*

Dynorphins are derived from prodynorphin. Dynorphins are found in hypothalamus, posterior pituitary and duodenum. Dynorphins are of two types, α- and β-dynorphins.

iii. *Endorphins*

Endorphins are the large peptides derived from the precursor pro-opiomelanocortin. Endorphins are predominant in diencephalic region particularly hypothalamus and anterior and intermediate lobes of pituitary gland. Three types of endorphins are recognized, α-, β- and γ-endorphins.

■ COTRANSMISSION AND COTRANSMITTERS

Cotransmission is the release of many neurotransmitters from a single nerve terminal. Cotransmitters are the

TABLE 141.4: Non-opioid neuromodulators

Name	Site of secretion	Action
Bradykinin	Blood vessels, kidneys	Vasodilator
Substance P	Brain, spinal cord, retina peripheral nerves and intestine	Mediates pain. Regulates anxiety, stress, mood disorders, neurotoxicity, nausea and vomiting. Causes vasodilatation.
Secretin	Cerebral cortex, hypothalamus, thalamus, olfactory bulb, brainstem and small intestine	Inhibits gastric secretion and motility
CCK	Cerebral cortex, hypothalamus, retina and small intestine	Contracts gallbladder Inhibits gastric motility Increases intestinal motility
Gastrin	Hypothalamus, medulla oblongata, posterior pituitary and gastrointestinal (GI) tract	Increases gastric secretion and motility Stimulates islets in pancreas
VIP	Cerebral cortex, hypothalamus, retina and intestine	Causes vasodilatation
Motilin	Cerebral cortex, cerebellum, posterior pituitary and intestine	Stimulates intestinal motility
Neurotensin	Hypothalamus and retina	Inhibits pain sensation Decreases food intake
Vasopressin	Posterior pituitary, medulla oblongata and spinal cord	Causes vasoconstriction
Oxytocin	Posterior pituitary, medulla oblongata and spinal cord	Stimulates milk ejection and uterine contraction
CRH	Hypothalamus	Stimulates release of ACTH
GHRH	Hypothalamus	Stimulates release of growth hormone
GHRP	Hypothalamus	Stimulates release of GHRH
TRH	Hypothalamus, other parts of brain and retina	Stimulates release of thyroid hormones
Somatostatin	Hypothalamus, other parts of brain, substantia gelatinosa and retina	Inhibits growth hormone secretion Decreases food intake
GnRH	Hypothalamus, preganglionic autonomic nerve endings and retina	Inhibits gonadotropin secretion
Endothelin	Posterior pituitary, brainstem and endothelium	Causes vasoconstriction
Angiotensin II	Hypothalamus, brainstem and spinal cord	Causes vasoconstriction
ANP	Hypothalamus, brainstem and heart	Causes vasodilatation Increases sodium excretion
BNP	Hypothalamus and heart	Causes vasodilatation Increases sodium excretion
CNP	Brain, myocardium, endothelium of blood vessels, GI tract and kidneys	Causes vasodilatation Increases sodium excretion
Neuropeptide Y	Medulla, hypothalamus and small intestine	Increases food intake Causes vasoconstriction Increases enteric blood flow
Ghrelin	Hypothalamus, stomach, pituitary, kidney and placenta	Promotes GH release Induces appetite and food intake Stimulates gastric emptying

ACTH = Adrenocorticotropic hormone, ANP = Atrial natriuretic peptide, BNP = Brain natriuretic peptide, CCK = Cholecystokinin. CNP = C-type natriuretic peptide, CRH = Corticotropin-releasing hormone, GHRH = Growth hormone-releasing hormone, GHRP = Growth hormone-releasing polypeptide, GnRH = Gonadotropin-releasing hormone, TRH = Thyrotropin-releasing hormone, VIP = Vasoactive intestinal polypeptide.

TABLE 141.5: Opioid neuromodulators

Name	Site of secretion	Action
Enkephalins	Many parts of brain, substantia gelatinosa and retina	Inhibit pain sensation
Dynorphins	Hypothalamus, posterior pituitary and duodenum	
β-endorphin	Thalamus, hypothalamus, brainstem and retina	

neurotransmitter substances that are released in addition to primary transmitter at the nerve endings.

For many years, it was believed that each neuron releases only one neurotransmitter substance from its terminals. Now it is known that some of the neurons release many neurotransmitter substances. It is also believed that the additional neurotransmitters, i.e. the cotransmitters modulate the effects of primary neurotransmitters.

Some of the primary neurotransmitters act as cotransmitters in other nerve endings.

Examples of cotransmitters:

1. Calcitonin
2. Dopamine
3. Dynorphin
4. GABA
5. Gene-related peptide
6. Glutamate
7. Glycine
8. Neuropeptide Y
9. Substance P
10. Vasoactive intestinal polypeptide (VIP).