CHAPTER 3

SYNAPTIC TRANSMISSION AND PROCESSING OF SIGNALS IN THE CNS

The synapses are the sites of junction between neurons. The axon of the *presynaptic neuron* divides into about 2000 branches on the average, each of which ends by a knob called the ***synaptic knob***. A large number of these knobs terminate on the ***dendrites, soma and axon of the postsynaptic neuron*** (e.g. about 10000 knobs terminate on each spinal motor neuron), and at the sites of contact, the knobs are separated from the postsynaptic membranes by gaps filled with ECF called the ***synaptic clefts*** (figure 21).

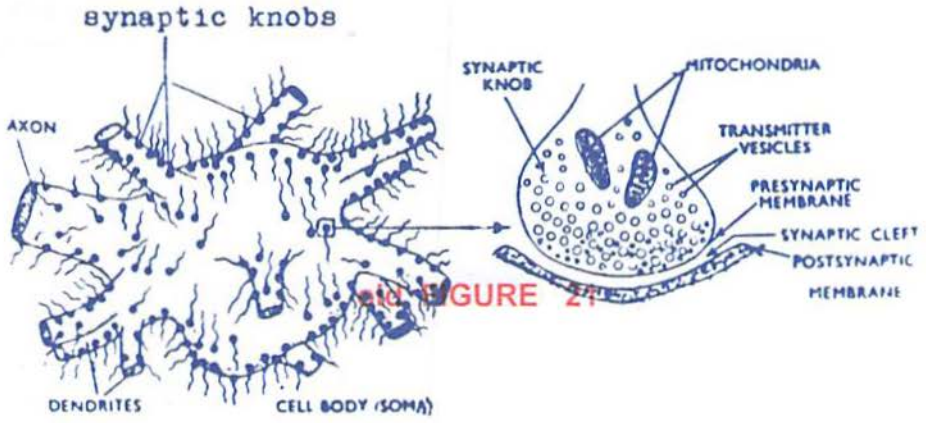

Figure 21 : A spinal motor neuron (AHC) and a synaptic knob on the right.

TYPES OF SYNAPSES

(1) Chemical synapses : These are the ***majority*** in the CNS. The synaptic knobs contain ***vesicles in which neurotransmitters are synthesized***, and are rich in ***mitochondria*** that provide the required energy. Stimulation of the presynaptic neurons leads to release of the neurotransmitters from these knobs which affect the excitability of the postsynaptic neurons (see below).

(2) Electrotonic (or gap junction) synapses : These are ***few*** but more rapid. The membranes of the pre and post-synaptic neurons come close to each other and ***gap junctions form between them***. Such junctions constitute ***low-resistance bridges*** through which ions can pass easily, allowing transmission of the depolarization waves directly from one neuron to the other.

(3) Conjoint synapses : These are ***rare*** in the nervous system, and the transmission of signals across them occurs ***both chemically and electrically***.

Mechanism of impulse transmission in chemical synapses

(1) Release of transmitters : Depolarization of the knobs leads to opening of voltage-gated Ca^{2+} channels, which allows ***Ca^{2+} influx*** into the knobs. *Ca^{2+} causes fusion of the vesicles with the knob's membrane* at specific ***active zones***, which then rupture leading to release of the transmitter by ***exocytosis*** into the synaptic clefts. The process of fusion involves interaction between 2 proteins, one in the vesicle membrane (= ***synaptobrevin***) and the other in the knob's membrane (= ***syntaxin***). Recently, it was also found that certain proteins called **neurexins** bind the membranes of the presynaptic and postsynaptic neurons together.

(2) Action of transmitters : The transmitter binds to specific receptors in the postsynaptic membrane. This triggers either opening or closure of specific ***ligand gated ion channels*** in that membrane, resulting in electric changes called ***postsynaptic potentials*** (= ***PSPs***) which lead to either excitation or inhibition of the postsynaptic neuron, depending on the nature of the released transmitter (see below).

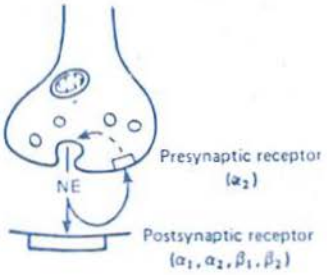

Figure 22 : Presynaptic and postsynaptic receptors at a noradrenergic nerve ending (NE = noradrenaline).

TYPES OF SYNAPTIC RECEPTORS

(1) Presynaptic receptors : These often ***inhibit the release of the neurotransmitters*** e.g. there are ***alpha $_2$ presynaptic receptors*** at the noradrenergic synaptic knobs that are excited by the released transmitter itself but they inhibit its further release (figure 22).

(2) Postsynaptic receptors : There are usually several postsynaptic receptors for each neurotransmitter e.g. :

1. Acetylcholine has 2 types of receptors : Nicotinic and Muscarinic (the latter are 5 types termed M_1 to M_5 receptors).

2. Noradrenaline has 2 types of alpha receptors (1 and 2, each of which has 3 types) and 3 types of beta receptors (1, 2 and 3).

3. Dopamine has 5 types of receptors (called D_1 to D_5 receptors).

4. Serotonin has 7 types of receptors.
5. GABA has 3 types of receptors (A and B in the CNS, and C in the retina).
6. Histamine has 3 types of receptors(called H_1, H_2 and H_3 receptors).

TYPES OF POSTSYNAPTIC POTENTIALS

(A) Excitatory postsynaptic potential (EPSP)

This is a state of *transient partial depolarization in the postsynaptic membrane during which the excitability of the postsynaptic neuron to other stimuli is increased.* It occurs in excitatory synapses (at which the transmitter is excitatory e.g. acetylcholine), and is due mainly to an ***increase in*** Na^+ ***or*** Ca^{+2} ***influx*** secondary to opening of their channels.

(B) Inhibitory postsynaptic potential (IPSP)

This is a state of *transient hyperpolarization in the postsynaptic membrane during which the excitability of the postsynaptic neuron to other stimuli is decreased.* It occurs in inhbitory synapses at which the transmitter is **glycine** (see below), and is due mainly to an ***increase in*** Cl^- ***influx***. However, some IPSPs are produced by ***opening of*** K^+ ***channels*** (which increases K^+ efflux) while others can be produced by *closure of* Na^+ *or* Ca^{+2} *channels.*

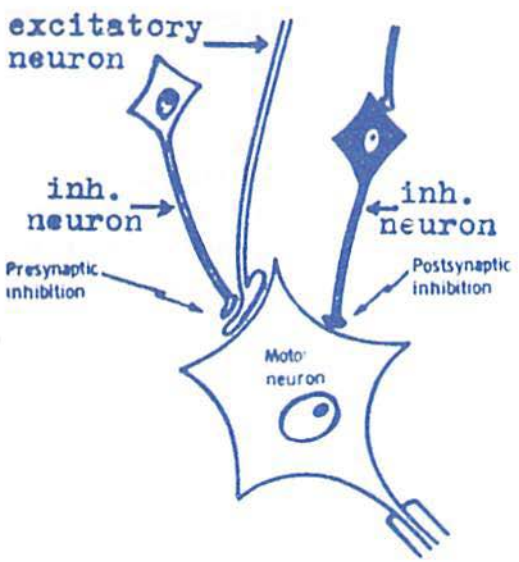

Figure 23 : Types (mechanisms) of synaptic inhibition.

TYPES (MECHANISMS) OF SYNAPTIC INHIBITION

(1) Postsynaptic inhibition

This is the ***commonest mechanism of inhibition*** in the CNS. The terminal knobs of the inhibitory neurons are in direct contact with the postsynaptic neuron (figure 23). Their neurotransmitter is **glycine,** which induces **IPSP** ***by increasing Cl⁻ influx*** (see above).

(2) Presynaptic inhibition

In this type of inhibition, the terminal knobs of the inhibitory neurons ***terminate on the excitatory nerve endings*** (= axo-axonal synapses) *and not on the postsynaptic neurons* (figure 23). It occurs ***in the dorsal horns*** where **enkephalinergic neurons** block pain transmission (refer to the ***analgesia system***, page 35) as well as in other parts in the nervous system in which the transmitter is **GABA**. These inhibitory transmitters decrease the release of the transmitter from the excitatory nerve terminals ***by either a direct effect or by decreasing Ca^{2+} influx*** (thus decreasing post-neuronal excitation).

** *GABA produces the latter effect by decreasing the size of the action potential in the excitatory endings* (which decresaes opening of the Ca^{2+} channels and Ca^{2+} influx). *At the GABA $_A$ & $_C$ receptors, this occurs by increasing Cl- influx while at the GABA $_B$ receptores, it occurs by increasing K^+ efflux*

SUMMATION OF POSTSYNAPTIC POTENTIALS (PSPs)

The PSP (whether excitatory or inhibitory) produced by activity in a single synaptic knob is normally very small and ineffective. However, it is ***not an all or none response*** and can be summated by 2 ways :

(1) Spatial summation : This is more common in the CNS, and is the summation of the PSPs produced by *activation of many synaptic knobs* **at the same time** (commonly *as a result of simultaneous excitation of multiple presynaptic neurons*).

(2) Temporal summation : This is the summation of the PSPs produced by *repeated activation of one synaptic knob* (by continuous stimulation of a single presynaptic neuron). In this case, a new PSP must develop before the previous PSP decays (therefore, the time between successive stimuli must be *less than 15 milliseconds*, which is the time after which a single PSP decays)

** Both types of summation may coexist (= ***temporo-spatial summation***) if several presynaptic neurons are successively stimulated rapidly one after the other at intervals not exceeding 15 milliseconds.

THE CENTRAL EXCITATORY & CENTRAL INHIBITORY STATES

Thousands of excitatory and inhibitory synaptic knobs normally converge on postsynaptic neurons. Therefore, both EPSPs and IPSPs commonly occur simultaneously, and the ***result depends on the algebraic sum of the*** produced ***depolarizing and hyperpolarizing effects***. Predominance of the former produces a central excitatory state (CES) while predominance of the latter produces a central inhibitory state (CIS).

The central excitatory state favours firing of action potentials from the postsynaptic neurons. The portion in these neurons with the lowest threshold for production of action potentials is the ***initial segment of the axon*** (at and just beyond the axon hillock). For this reason, ***the most rapid transmission of signals normally occurs at the axo-axonic synapses***.

THE PROPERTIES OF SYNAPTIC TRANSMISSION

(1) One way conduction (forward direction) : In synapses, impulses are conducted ***only from the presynaptic to the postsynaptic neurons*** (because the chemical transmitters are present only in the presynaptic knobs).

(2) Delayed conduction (synaptic delay) : There is a delay of impulse transmission in synapses of about ***0.5 millisecond*** due to the time required for release of the neurotransmitter, its diffusion through the synaptic cleft and its binding to and activation of the postsynaptic receptors.

** The **number of synapses in a reflex can be calculated as follows :** The ***total reflex time*** and the time of conduction in the ***afferent and efferent nerves*** are determined. The difference between both represents the time of conduction in the CNS, and is known as the ***central delay***. The number of synapses in the reflex = **Central delay / Synaptic delay** (e.g. if the central delay is 3 milliseconds, the number of synapses = 3 / 0.5 = 6 synapses).

(3) Synaptic fatigue : This is slowing or failure of impulse conduction across synapses that occurs after repetitive stimulation of presynaptic neurons. It may be due to depression of the postsynaptic neurons but it is believed to be primarily due to ***depletion of the neurotransmitter***.

(4) Synaptic afterdischarge : This is continuation of discharge from the postsynaptic neurons for some time ***after stopping stimulation of presynaptic neurons***. It is due to *persistence of the central excitatory state* produced by the initial stimulus, and it leads to prolongation of discharge of signals from motor neuronal pools (page 48).

(5) Summation of postsynaptic potentials : This occurs by both spatial and temporal mechanisms (page 40).

(6) High sensitivity to the following :

1- Blood pH : Alkalosis increases while acidosis decreases synaptic transmission. Thus, a rise of blood pH from 7.4 to 7.8 leads to convulsions while its fall is associated with drowsiness (or coma in severe acidosis).

2- Blood O_2 level : Hypoxia decreases synaptic transmission, so unconsciousness occurs if the cerebral circulation stops for only 3-5 seconds.

3- Drugs and chemicals :

A- ***Drugs that increase synaptic transmission*** **:**

- Theophylline, caffeine and theobromine.
- Strychnine and tetanus toxin (by blocking the action of glycine).
- Picrotoxin (by blocking the action of GABA).

B- ***Drugs that decrease synaptic transmission :***

- Anesthetic drugs.
- Anti-anxiety and tranquilizer drugs (e.g. diazepam), hypnotic drugs (e.g. barbiturates) and alcohol. All these act by facilitating the action of GABA.

(7) Plasticity and learning :

This means changes in the strength of synaptic transmission (which represent forms of ***learning & memory***, page 129). Such changes are ***presynaptic and postsynaptic***, and they include **potentiation, depression & sensitization**

Synaptic potentiation (or facilitation)

This is production of high-amplitude EPSPs in response to stimulation. It occurs after a brief period of *rapidly repeated stimulation of the presynaptic neuron* (= tetanizing train of stimuli), and is 2 types :

1- Short-term potentiation (= post-tetanic potentiation)

This lasts up to one minute, and is due to accumulation of excess Ca^{2+} in the presynaptic knobs as a result of the repeated stimulation (which increases the release of the neurotransmitter, and in turn increases the EPSP).

2- Long-term potentiation (LTP)

This specially occurs in the ***hippocampus*** where the excitatory transmitter is ***glutamate***. It lasts a few hours or days, and ***both the pre and postsynaptic neurons participate in its production***. The presynaptic neuron releases glutamate which increases Ca^{2+} influx in the postsynaptic neuron, thus increasing the EPSP. The postsynaptic neuron in turn releases a chemical signal (? NO) that causes more glutamate secretion from the presynaptic neuron.

Synaptic depression

This is a decrease in the response of postsynaptic neurons, and is 2 types :

1- **Habituation :** This is a ***gradual decrease of the postsynaptic response*** when a stimulus to the presynaptic neuron is repeated over and

PROCESSING OF SIGNALS IN THE CNS

The CNS is made up of hundreds of neuronal pools (i.e. collections of neurons). Input signals *do not affect these pools equally* (= ***fractionation of pools***) *and also do not affect all neurons in the same pool equally*. When an ***input signal*** enters a pool, it is processed so as to produce an ***appropriate output signal***. This occurs through ***divergence, convergence, prolongation, shortening or sharpening of signals***.

The discharge and facilitated zones of neuronal pools

The neurons in a certain pool that are excited by an input neuron constitute the **excitation field of that neuron**. The central neurons in this excitation field receive a large number of nerve terminals, so they reach the threshold of firing, and consequently *they discharge impulses*. For this reason, the **central zone in an excitation field is called the firing or discharge zone**.

On the other hand, the peripheral neurons in the excitation field receive a smaller number of nerve terminals, ***so they are only facilitated*** but *do not discharge impulses*. Accordingly, the peripheral zone (i.e. fringe) in an excitation field is called the **facilitated zone or subliminal fringe** (figure 25).

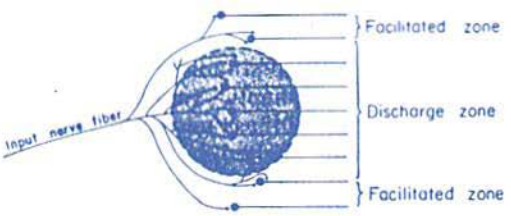

Figure 25 : Discharge and facilitated (subliminal) zones in a neuronal pool.

Divergence of signals in neuronal pools

This is the spread of signals from one input neuron to many output neurons, and it is 2 types :

(1) Divergence in the same tract : This is characteristic of *the cortico-spinal* (= *pyramidal*) *tract,* in which a single cerebral cortical cell can excite about 1000 muscle fibres (figure 26 A).

(2) Divergence into multiple tracts : This is spread of the input signal in 2 separate directions (figure 26 B) e.g. in the dorsal column of spinal cord, the input signals diverge into the spinocerebellar and gracile and cuneate tracts.

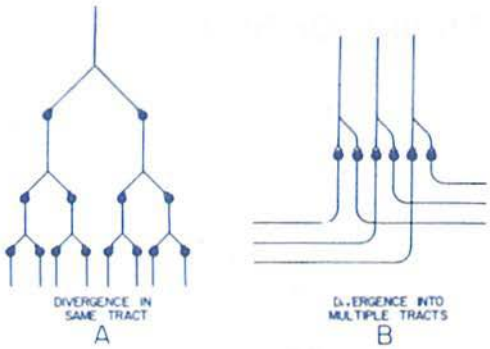

Figure 26 : Divergence in the same tract (A) and in multiple tracts (B).

Convergence of signals in neuronal pools

This is the collection of signals from multiple input neurons to a single output neuron, and it is 2 types :

(1) Convergence from a single source (figure 27 A).

(2) Convergence from multiple sources (figure 27 B).

Both types lead to **summation of impulses**, which is essential for excitation of postsynaptic neurons (page 40).

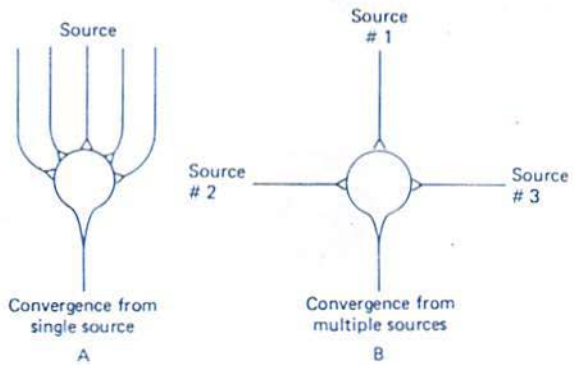

Figure 27 : Convergence from a single source (A) and multiple sources (B).

Prolongation of signals in neuronal pools

Excitatory input signals can lead to a prolonged output discharge even after they stop. This is called **afterdiseharge** and it can occur by 2 ways :

(1) Synaptic after-discharge (page 41).

(2) Interneuronal barrages (circuits) : These are 2 types :

(a) Parallel (= multiple or open-chain) circuits : The input signal reaches the output neuron in the form of successive impulses via a number of interneurons that run in parallel (figure 28), resulting in a continued discharge from the output neuron for several milliseconds after the input signal stops.

(b) Reverberatory (= oscillatory or closed-chain) circuits : In this type, the output neuron is repeatedly stimulated through closed circuits of interneurons called ***reverberators*** by a ***positive feedback mechanism*** as follows : Collaterals from the interneurons feedback by way of the reverberators to re-excite the output neuron again and again after the input signal stops (most right in figure 28), and this continues for variable periods, after which it stops due to either fatigue of the synaptic transmission or by the effect of an inhibitory input (see below).

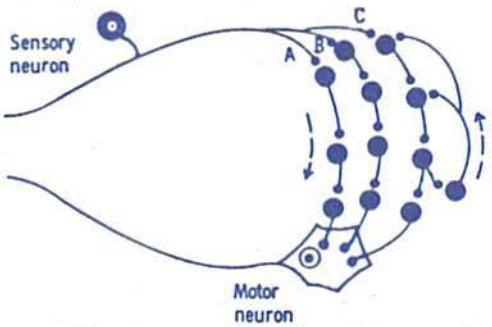

Figure 28 : Interneuronal barrages. Reverberators are shown most right.

Shortening of signals in neuronal pools

An undesired prolonged discharge from a neuronal pool can be prevented by **negative feedback inhibition :** A collateral from an excitatory neuron stimulates an inhibitory interneuron which turns back and inhibits the same excitatory neuron. This function is specially performed by the **Renshaw cells** (figure 29).These cells are *inhibitory interneurons in the anterior horns of the spinal cord gray matter*. The axon of the alpha spinal motor neuron in the anterior horn gives an excitatory ***cholinergic recurrent collateral*** that

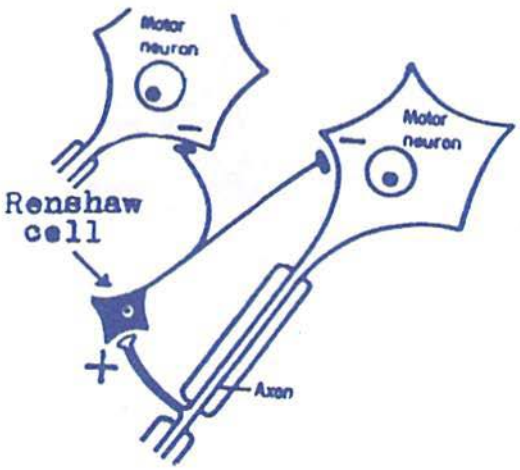

Figure 29 : Negative feedback inhibition by the Renshaw cells.

stimulates a Renshaw cell, and this cell in turn sends signals that inhibit the following neurons through releasing **glycine :**

(a) The original motor neuron, leading to its inhibition (that is commonly called ***negative feedback, collateral, recurrent or Renshaw inhibition***) which results in shortening of the output signals.

(b) The motor neurons in the surrounding area, leading to ***lateral inhibition*** of these neurons, which sharpens the output signals (see next).

** Another mechanism for shortening of signals is present in the cerebellum and is called **negative feed-forward inhibition** (page 108).

Sharpening of signals in neuronal pools

This helps to focus the activity of the output neurons, and it occurs through ***inhibiting the activity of neurons*** in the surrounding pools by one of the following mechanisms :

(1) Lateral inhibition : A collateral from the active output neuron stimulates an inhibitory interneuron which prevents activity in the surrounding neurons. This commonly occurs by the ***Renshaw cells*** (figure 29) as well as in the ***cerebellum*** (page 107) and the retina of the eye by the ***horizontal cells*** (refer to special senses)

(2) Reciprocal inhibition circuits : Such circuits characteristically coordinate many spinal reflexes. For example during the stretch reflex, the input fibres directly excite the motor neurons of the stretched muscle and simultaneously stimulate an interneuron that inhibits the surrounding neurons particularly those supplying the antagonist muscle (figure 30) resulting in sharpening of signals to the stretched muscle as well as its smooth contraction.

The same occurs during the withdrawal reflex (figure 33). The spinal inhibitory interneurons are short plump neurons with thick axons. They are called ***Golgi bottle neurons,*** and they produce direct postsynaptic inhibition.

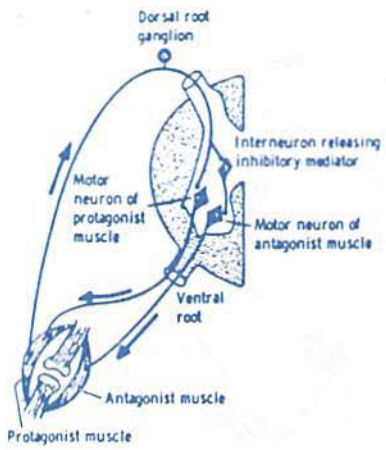

Figure 30 : A reciprocal inhibition circuit acting during the stretch reflex.