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INTRODUCTION TO NEUROPHYSIOLOGY
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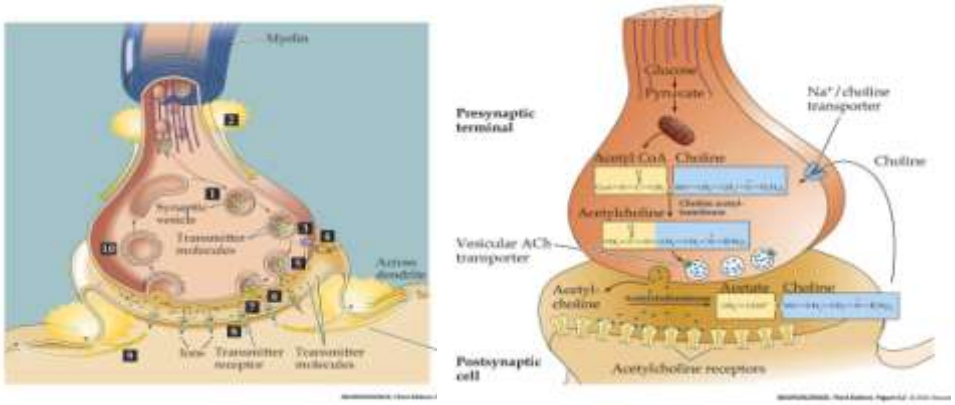
Junctions, Synapses & Neurotransmitters:

Synaptic Transmission at the NMJ



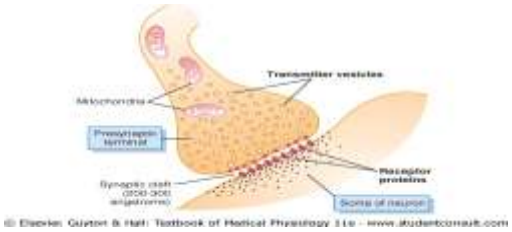
Synapses continued to be studied from many angles by physiologists and pharmacologists. However, real progress started to be made only when microelectrodes with very thin points could be manufactured. It was Sir John Carew Eccles (1903-1997), who was the pioneer in this area. Eccles started by studying the neuromuscular junction (NMJ) this was a favorite subject of early synaptologists, because NMJ is big, access to it is easy, and isolated preparations could be mounted with little effort.

Substances affect the Neuromuscular junction (NMJ);

1. Prevent Ach release at NMJ (Botulinum toxin)Botox
2. Competitive antagonist on Ach receptors (Tubocurarine), can be used as muscle relaxant in abdominal surgery.
3. Anti-cholinesterase substances;
   Nerve gas (Diisopropyl fluorophosphates)
   Neostigmine to diagnose or treat myasthenia gravis, and also used to terminate curare effect in surgery.

Types of Synapses:

1. Chemical Synapse: needs NT and transmit signals in one direction.



2. Electrical Synapses: rare in brain, no need for NT, instead they use gap junctions and they transmit signals in either direction.

Physiologic anatomy of the synapse:

1.Presynaptic terminals: when AP arrives the voltage gated Ca^{+2} channels open and lead to Ca^{+2} influx, the quantity of NT is directly related to the number of Ca^{+2} ions that enter. When Ca^{+2} enter the terminal they bind with special protein molecule on the inside surface of the terminal (release sites) this binding cause the release sites to open through the membrane allowing vesicles to release NT into cleft.

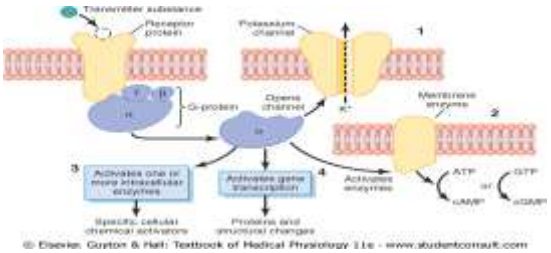
2.Postsynaptic neuron: function of receptor protein: Receptor protein contains two components:

1. Binding component
2. Ionophric component:

a. Ion Channel activation

b. Second messenger activator like G-protein and this will lead to

1. Opening ion channel for prolonged period
2. Activation of cAMP or cGMP
3. Activation of intracellular enzyme(s)
4. Activation of gene transcription which will cause new protein formation.



Factors affecting synaptic excitability;

1. Hypoxia and acidosis decrease synaptic transmission leading to coma.
2. Alkalosis greatly increase synaptic transmission and can precipitate epilepsy in susceptible persons,

caffeine in coffee, theophylline in tea and theobromine in cocoa increase synaptic transmission

Types of Neurotransmitters (NT):

1. Small molecule rapidly acting NT:

a. NT synthesized in the cytosol of the presynaptic terminal.
b. NT are absorbed by active transport to synaptic vesicles and stored until used upon arrival of AP.
c. Vesicles are recycled and used over and over again.
d. This type of NT causes the most acute response of CNS (sensory signals to the brain & motor signals to skeletal muscles).
e.g. Acetylcholine, Norepinephrine, Dopamine, Serotonin, Glycin, GABA, Glutamate and Nitric Oxide.

2. Large molecule slowly acting NT:

a. Synthesized by Ribosome in the soma, then to ER then to Golgi apparatus where they split and packaged into vesicles.
b. Transported to terminal by slow axonal streaming.
c. Vesicles are released in response to AP but they are autolyzed and are not reused.
d. They have much more prolonged action and they are a thousand or more times as potent as the small molecule NT and released in much smaller quantities.
e.g. Pituitary peptides, β - Endorphin, Leu - Enkephalin, Met - Enkephalin, Substance P, Gut peptides, Sleep peptides.....etc.

Excitatory Post-Synaptic Potential (EPSP):

Positive increase in voltage above the Resting Neuronal Potential (RNP) to a less negative value e.g. changing resting neuronal potential from -65 mv to - 45 mv. It is mainly due to opening of Na^+ channels leading to Na^+ influx, this occurs because the NT that is released from pre-synaptic terminal act on the membrane excitatory receptors and increase membrane permeability to Na^+. If EPSP is enough and can reach threshold then an AP is generated usually at the initial segment of the axon which contains 7 times as great a concentration of voltage gated Na^+ channels as does the soma.

Inhibitory Post-Synaptic Potential:

An increase in negativity beyond the RNP. It can take place as a result of opening Cl^- channels leading to Cl^- influx or opening K^+ channels and leading to K^+ efflux . Both Cl^- influx and K^+ efflux increase the degree of intracellular negativity (Hyperpolarization), leading to neuronal inhibition.

Summation:

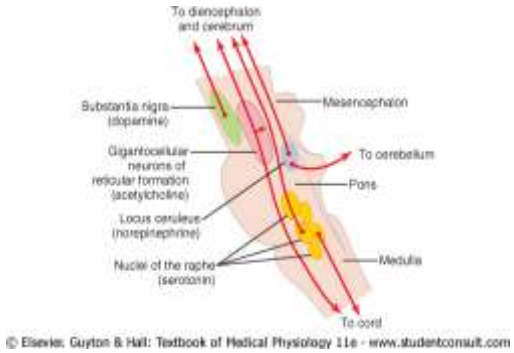
EPSP and IPSP are local potentials (Electrotonic potentials), they change the RNP by few mv and for few msec then they slowly decline. Single EPSP can never excite the neuron because single EPSP can change neuronal potential no more than 0.5 - 1 mv, in fact we need 10 -20 mv for the neuron to reach threshold and fire an AP at the initial segment of the axon. However many pre-synaptic terminals are usually stimulated together and due to low somal resistance they can summate. The effect of summing simultaneous pre-synaptic potentials by activating multiple terminals on widely spaced area of the neuronal membrane is called (Spatial Summation).
Summation can also occur, if successive discharges from a single pre-synaptic terminal that occur rapidly are summated, this type of summation is called (Temporal summation)
If an EPSP and an IPSP take place at the same time on a soma these two effects can partially or completely nullify each other.

Synaptic Fatigue:

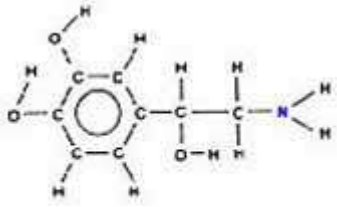
1. It is due to exhaustion of NT stores at the pre-synaptic terminals. Synaptic fatigue is an important characteristic of synaptic function because overexcited neurons within the brain will lose their excess excitability by synaptic fatigue. e.g. Epileptic seizure.
2. Synaptic fatigue may also be due to progressive inactivation of post-synaptic receptors and slow development of abnormal concentration of ions inside the post-synaptic neuronal cell.

NEUROHORMONAL CONTROL OF BRAIN:

They often persist for minutes or even hours & provide long periods of control. In human four systems were described:



1. The LOCUS CERULEUS & the NOREPINEPHRINE SYSTEM:



Norepinephrine

Norepinephrine (NE) is a neurotransmitter that plays a part in controlling alertness, attention, and memory. So if you are reading this lecture, and are having trouble concentrating, it could be because your brain is currently not producing enough norepinephrine. Going to get some coffee would help you to raise these levels, allowing concentration to return.

NE generally excites the brain to increase its activity, & may be inhibitory in a very few brain areas. This system play important role in causing dreaming (REM sleep).

Drugs that increase extracellular norepinephrine level elevates mood, while drugs that decrease it cause depression. In manic-depressive illness there is a genetic abnormality close to or in the gene on chromosome 11 that codes for Tyrosine hydroxylase, the rate limiting enzyme in catecholamine biosynthesis.

2. The SUBSTANTIA NIGRA & the DOPAMINE SYSTEM:

Dopamine (DA) is the neurotransmitter that plays a part in controlling movement, thought processes, emotions, and the pleasure centers of the brain. When a person physically works out or accomplishes a difficult task, the brain releases excess dopamine into certain areas of the brain. Any release of dopamine induces a sense of euphoria and wellbeing.

Destruction of the dopaminergic neurons in the substantia nigra is the basic cause of Parkinson's disease. Studies with Positron Emission Tomography (PET) indicate steady loss of dopamine receptors in the basal ganglia with age.

PET scanning of Schizophrenic patients indicate elevated level of D_2 receptors & chromosomal study in these patients indicate abnormality in chromosome 5 which may well be involved in dopaminergic system.

Amphetamines which stimulate secretion of dopamine & norepinephrine produces a psychosis resemble schizophrenia when administered in large doses. Phenothiazines tranquillizers are effective in the relief of the symptoms of schizophrenia through their ability to block D_2 dopamine receptors.

3.THE RAPHI NUCLEI & THE SEROTONIN SYSTEM:

Serotonin plays an important role in many behaviors including sleep, appetite, memory, sexual behavior, and mood. The chemical structure of serotonin closely resembles that of many hallucinogens. A hallucinogen like LSD can bind onto serotonin receptors, mimicking the actual neurotransmitter, resulting in unnatural stimulation in different areas of the brain. The actual serotonin neurotransmitter is structurally different than the other synaptic messengers of the brain.

When a person has a deficiency in brain serotonin levels, they are more likely to exhibit violent behavior, anxiety, depression, impulsiveness, and could have a propensity towards drug and alcohol abuse. When a person has higher levels of serotonin in the brain, they are less aggressive, mellow, and happier.

The raphe nucleus sends fibers to diencephalon & cerebrum to play an inhibitory role to help in causing normal sleep & selective depletion of serotonin in brain lead to Insomnia (inability to sleep). Serotonin may play a role in inhibiting transmission of pain in the SC.

The antidepressant drug, Prozac increases serotonin activity. Its main action is to increase serotonin transmission in the brain by inhibiting the reuptake of the neurotransmitter.

When a person does a drug like meth (Methamphetamine), that person's neurotransmitter levels can be affected. Dopamine, norepinephrine, and serotonin are all affected by meth and can suffer long-lasting damage even after just one trial with this dangerous drug. Wurtman has reported that people are more alert when their brains are producing the neurotransmitters dopamine and norepinephrine, while serotonin production in the brain has been associated with a more calming, anxiety-reducing effect (and even drowsiness in some people). A stable brain serotonin level is associated with a positive mood state. It appears that women have a greater sensitivity than men to changes in this brain chemical. Mood swings during the menstrual cycle and menopause are thought to be caused by hormonal changes that influence the production of serotonin.

How does diet play a role? The foods that increase the production of serotonin in the brain are high in carbohydrates. Many kinds of foods carbohydrates, such as candy, cereal, and pasta, can produce a temporary increase in brain serotonin—and a subsequent calming or anxiety-reducing effect. This explains why people may feel drowsy in the afternoon after eating a large meal of pasta, since a rise in serotonin in the brain can also lead to drowsiness. Carbohydrates affect brain serotonin because they increase the amount of tryptophan in the brain. Tryptophan is the amino-acid precursor of serotonin. The two other important brain chemicals that appear to be influenced by foods, dopamine and norepinephrine, produce a feeling of alertness, an increased ability to concentrate, and faster reaction times. There are two possible mechanisms for how this happens: (1) serotonin production is blocked by the consumption of protein-rich foods, resulting in increased alertness or concentration, or (2) levels of dopamine and norepinephrine are increased by the consumption of protein-rich foods.

4. THE GIGANTOCELLULAR NEURONS OF THE RETICULAR EXCITATORY AREA & THE ACETYLCHOLINE SYSTEM:

Send excitatory fibers to the higher centers which lead to awake & excited mind. It also sends excitatory fibers to SC through the Reticulo-spinal tract. Acetylcholine is distributed throughout the CNS with high concentration in cerebral cortex, thalamus, & various nuclei in the basal forebrain. Cholinergic neurons projecting to hippocampus are involved in memory, while projections from nucleus basalis of Meynert, amygdala & the entire neocortex are involved in motivation, perception & cognition. In Alzhiemer's disease there is extensive cell loss of these projections leading to Dementia. In basal ganglia acetylcholine is excitatory & dopamine is inhibitory, therefore loss of the dopamine alters the cholinergic-dopaminergic balance.

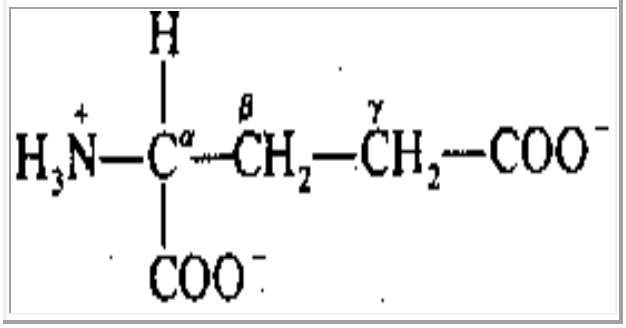
OTHER NEUROTRANSMITTERS:

Enkephalins, GABA, Glutamate, Vasopressin, ACTH, Epinephrine, Endorphine, Angiotensine 2, Neurotensin.....etc.

GABA (gamma amino butyric acid); is an inhibitory mediator in the brain & retina. Two different receptors for GABA were studied, GABAα that open Cl^- channels, while GABAβ increase K^+ conductance in K^+ channels. The effect of GABA on Cl^- conductance is facilitated by Benzodiazepins (Valium). The vitamin B6 derivative pyridoxal phosphate is a cofactor in the synthesis of GABA, which is why seizures occur in Vitamin B6 deficiency. Alcohol & Barbiturates act by facilitating conductance of Cl^- through Cl^- channels.

GLUTAMICACID (GLUTAMATE)

Glutamate



Glutamate is the most common neurotransmitter in the brain. It is always excitatory, usually due to simple receptors that increase the flow of positive ions by opening ion-channels. Possibly the most complicated of all neurotransmitter receptors is the NMDA glutamate receptor. N-Methyl-D-Aspartate is a synthetic chemical not naturally found in biological systems, but it binds specifically to the NMDA glutamate receptor (receptors are frequently named for artificial substances that bind to the receptor with higher specificity than their natural neurotransmitter ligands). The NMDA receptor is the only known receptor which is regulated both by a ligand (glutamate) and by voltage. There are at least 5 binding sites which regulate NMDA receptor activity, *ie*, sites for (1) glutamate (2) glycine (3) magnesium (4) zinc and (5) a site that binds the hallucinogenic substance phencyclidine (Phenylcyclohexyl piperidine) (PCP, "angel dust"). Phencyclidine can induce psychosis -- an NMDA effect that is difficult to explain. NMDA receptors have a capacity for an activity-dependent increase in synaptic efficiency known as LTP (Long-Term Potentiation), which may be crucial to some forms of learning & memory. Inhibition of NMDA activity (and LTP) is believed to be an important part of the way ethanol affects brain functions. NMDA receptors are most densely concentrated in the cerebral cortex hippocampus, amygdala, & basal ganglia. They are particularly vulnerable to glutamic acid excitotoxicity, *ie*, damaging effects due to excessive excitatory neurotransmitter release. Both aspartic acid & glutamic acid (the two amino acids having 2 carboxyl groups -- the "acidic amino acids") have the capacity for destroying neurons when released in excessive amounts. Glutamate released into synapses is either reabsorbed directly into neurons, or is soaked-up by astrocytes (glial cells) which convert the glutamate into glutamine (a molecule which cannot cause excitotoxicity). The glutamine can then be safely transported back to neurons for re-conversion into glutamate. Excitotoxicity due to glutamic acid is a major destructive process seen in strokes and other forms of brain ischemia.

Nitric oxide; It is synthesized almost instantly as needed, and then diffuses out of the presynaptic terminals rather than being released in vesicular packets. In the postsynaptic neurons, it usually does not greatly alter the membrane potential but instead changes intracellular metabolic functions that modify neuronal excitability for seconds, minutes or longer. Nitric oxide may contribute to LTP, and play a role in behavior and memory.