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Q1: Explain in detailed Neurotransmitters process ?

Ans: Neurotransmitters;

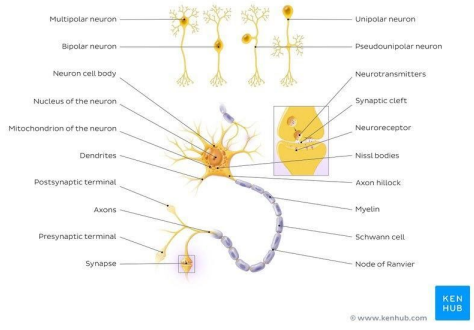
Neurotransmitters are substances which neurons use to communicate with one another and with their target tissues in the process of synaptic transmission (neurotransmission).

Neurotransmitters are synthetized in and released from nerve endings into the synaptic cleft. From there, neurotransmitters bind to receptor proteins in the cellular membrane of the target tissue. The target tissue gets excited, inhibited, or functionally modified in some other way.

There are more than 40 neurotransmitters in the human nervous system; some of the most important are acetylcholine, norepinephrine, dopamine, gamma-aminobutyric acid (GABA), glutamate, serotonin, and histamine.

Mechanism of neurotransmission;

Neurons communicate with their target tissues at synapses into which they release chemical substances called neurotransmitters (ligands). As this communication is mediated with chemical substances, the process is called chemical neurotransmission and happens within chemical synapses.



Each synapse Consist of :

Presynaptic membrane – membrane of the terminal bouton (axon ending) of the presynaptic nerve fiber
Postsynaptic membrane – membrane of the target cell
Synaptic cleft – a gap between the presynaptic and postsynaptic membranes
Inside the terminal bouton of the presynaptic nerve fiber, numerous vesicles that contain neurotransmitters are produced and stored. When the presynaptic membrane is depolarized by an action potential, calcium voltage-gated channels open (found in the membranes of the terminal buttons). This leads to an influx of calcium ions into the terminal bouton, which changes the state of certain membrane proteins in the presynaptic membrane, and results in exocytosis of neurotransmitters from the terminal bouton into the synaptic cleft.
After crossing the synaptic cleft, neurotransmitters bind to their receptors on the postsynaptic membrane. Once the neurotransmitter binds to its receptor, the ligand-gated channels of the postsynaptic membrane either open or close. These ligand-gated channels are ion channels, and their opening or closing alters the permeability of the postsynaptic membrane to calcium, sodium, potassium, and chloride ions. This leads to a stimulatory or inhibitory response.
If a neurotransmitter stimulates the target cell to an action, then it is an excitatory neurotransmitter acting in an excitatory synapse. On the other hand, if it inhibits the target cell, it is an inhibitory neurotransmitter acting in an inhibitory synapse. So, the type of the synapse and the response of the target tissue depends on the type of neurotransmitter. Excitatory neurotransmitters cause depolarization of the postsynaptic cells and generate an action potential; for example acetylcholine stimulates muscle contraction. Inhibitory synapses cause hyperpolarization of the target cells, leading them farther from the action potential threshold, thus inhibiting their action; for example GABA inhibits involuntary movements.

The neurotransmitter released into the synaptic cleft acts for a very short duration, only minutes or even seconds. It is either destroyed by enzymes, such as acetylcholine esterase, or is reabsorbed into the terminal button of the presynaptic neuron by reuptake mechanisms and then recycled. The best-known neurotransmitters responsible for such fast, but short-lived excitatory action are

acetylcholine, norepinephrine, and epinephrine while GABA is the major inhibitory neurotransmitter.

Disorders Related To Neurotransmitters;

Alzheimer's disease

Alzheimer's disease is a neurodegenerative disorder characterized by learning and memory impairments. It is associated with a lack of acetylcholine in certain regions of the brain.

Depression

Depression is believed to be caused by a depletion of norepinephrine, serotonin, and dopamine in the central nervous system. Hence, pharmacological treatment of depression aims at increasing the concentrations of these neurotransmitters in the central nervous system.

Schizophrenia

Schizophrenia, which is a severe mental illness, has been shown to involve excessive amounts of dopamine in the frontal lobes, which leads to psychotic episodes in these patients. The drugs that block dopamine are used to help schizophrenic conditions.

Parkinson's disease

The destruction of the substantia nigra leads to the destruction of the only central nervous system source of dopamine. Dopamine depletion leads to uncontrollable muscle tremors seen in patients suffering from Parkinson's disease.

Q2 What does direct and indirect cholinergic agent means? Explain therapeutic application and adverse effects of cholinergic agents in details?

Ans: Direct and indirect Cholinergic Agent;

1; Direct Cholinergic Agent;

- These Drugs directly bind and activate nicotinic and muscarinic receptor with variable amount of selectivity.

2; Indirect Cholinergic Agent ;

- These drugs inhibit anti cholinesterase the enzymes which distroy acetylcholine secreted into the synapse by the Cholinergic neuron. By inhibiting destruction these drugs extend the half life of synaptic acetylcholine and thus boost systemic Cholinergic activity.

Therapeutic Uses:

The drug increases intestinal and bladder motility which serve as it therapeutic action in atony of either organ placed topically in the eye, it produces miosis and spasm of accommodation as well as a lowering of intraocular pressure it is used to treat glucoma but pilocarpine is more effective.

Adverse Effects of Cholinergic drugs:

- Slow heart beat. Possibly leading to cardiac arrest
- Muscles weakness, muscles cramps, muscles pain.
- Convulsions.
- Weak breathing, inability to breathe
- Increase stomach acid and saliva.

Q3;(a)Differentiate between right heart failure and left heart failure ?
(b)Summarize the pharmacotherapy of heart failure?

Ans: In heart failure, the heart can no longer pump enough blood around the body. The heart muscle is either too weak or not elastic enough. Different parts of the heart may be affected too. The type of medication people use for the treatment of heart failure will depend on the type of heart failure they have.

Left-sided heart failure: The left ventricle of the heart no longer pumps enough blood around the body. As a result, blood builds up in the pulmonary veins (the blood vessels that carry blood away from the lungs). This causes shortness of breath, trouble breathing or coughing – especially during physical activity. Left-sided heart failure is the most common type.

Right-sided heart failure: Here the right ventricle of the heart is too weak to pump enough blood to the lungs. This causes blood to build up in the veins (the blood vessels that carry blood from the organs and tissue back to the heart). The increased pressure inside the veins can push fluid out of the veins into surrounding

tissue. This leads to a build-up of fluid in the legs, or less commonly in the genital area, organs or the abdomen (belly).

b; Pharmacotherapy of heart failure;

Most patient with symptomatic systolic heart failure should be routinely treated with an angiotensin converting enzyme ACE inhibitors, a beta-blocker, and a diuretic. The benefit of these medication on slowing HF progression, reducing morbidity and mortality, and improving symptoms and clearly established. Patient should be treated with a diuretic if there is evidence of fluid retention. Treatment with digoxin may also be considered to improve symptoms and reduce hospitalization.

Q4)Differentiate between primary and secondary hypertension?
a)Explain the effect of renin on hypertension
b)What is the importance of pharmacological treatment of hypertension ?

Ans: Primary Hypertension;

Primary hypertension has no single known cause but several mechanisms are linked to altered pathways in BP control. These are genetic factors, diet especially increased salt (sodium chloride) intake, obesity, insulin resistance, endothelial dysfunction, chronic excess alcohol, ageing, stress and sedentary lifestyle.

The pressure against the blood vessel walls is affected by cardiac output and peripheral resistance. Altered pathways in BP control leads to sustained constriction of the arterioles (microscopic blood vessels in the circulation) resulting in increased peripheral resistance in the blood vessels. As the heart continues to pump normally, the pressure in the whole arterial system rises. This normally has no outward symptoms for the individual, unless very high.

Secondary Hypertension:

In secondary hypertension BP is raised due to a known underlying cause:

Renal disorders (e.g. chronic pyelonephritis, diabetic nephropathy).

Vascular disorders (e.g. coarctation of the aorta).

Endocrine disorders (e.g. primary hyperaldosteronism).

Drugs (e.g. alcohol, cocaine)

Miscellaneous causes (e.g. scleroderma, obstructive sleep apnoea).

a: **Effect of Renin on Hypertension :**

The renin-angiotensin system or RAS regulates blood pressure and fluid balance in the body. When blood volume or sodium levels in the body are low, or blood potassium is high, cells in the kidney release the enzyme, renin. Renin converts angiotensinogen, which is produced in the liver, to the hormone angiotensin I. An enzyme known as ACE or angiotensin-converting enzyme found in the lungs metabolizes angiotensin I into angiotensin II. Angiotensin II causes blood vessels to constrict and blood pressure to increase. Angiotensin II stimulates the release of the hormone aldosterone in the adrenal glands, which causes the renal tubules to retain sodium and water and excrete potassium. Together, angiotensin II and aldosterone work to raise blood volume, blood pressure and sodium levels in the blood to restore the balance of sodium, potassium, and fluids. If the renin-angiotensin system becomes overactive, consistently high blood pressure results.

b: Pharmacological Treatment of hypertension :

There are several types of drugs used to treat high blood pressure, including:

- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin II receptor blockers (ARBs)
- Diuretics
- Beta-blockers
- Calcium channel blockers
- Alpha-blockers
- Alpha-agonists
- Renin inhibitors

Combination medications

Diuretics are often recommended as the first line of therapy for most people who have high blood pressure.

Q5:Explain the effects and adverse effects of organic nitrates in angina pectoris.

a)Write down the treatment algorithm for improving symptoms of stable angina.

Ans)

Nitrates are very effective antianginal and anti-ischaemic agents. Provision of a long nitrate-free interval or low plasma nitrate levels prior to the morning dose prevents the loss of clinical efficacy by preventing the development of tolerance. However, side effects during nitrate therapy are common. Headache is the most common side effect of nitrates; often dose-related and reported by up to 82% of patients in placebo-controlled trials. Nearly 10% of patients are unable to tolerate nitrates due to disabling headaches or dizziness. In others, headaches are mild-to-moderate in severity and either resolve or diminish in intensity with continued nitrate

therapy. Nitrate-induced hypotension is common, but often asymptomatic. In rare instances, nitrate-induced hypotension is severe and accompanied by marked slowing of the heart rate and syncope. Use of nitrates in patients who experience syncope after administration of nitrates is contraindicated. Nitrates rarely cause coronary steal and myocardial ischaemia. Nitrate rebound may occur and patients may experience nocturnal anginal episodes during intermittent therapy with nitroglycerin patches. Administration of nitrates is contraindicated with concomitant use of phosphodiesterase-5 inhibitors used for the treatment of erectile dysfunction, as combination therapy may lead to profound hypotension and even death. There are disturbing observational reports in the literature that continuous, prolonged use of nitrates may lead to increased mortality and recurrent myocardial infarctions. Large, randomised, placebo-controlled studies are needed to confirm or refute these reports; until then, the use of nitrates to treat angina is here to stay.

Treatment algorithm for improving symptoms of stable Angina;

Stable angina pectoris is characterised by typical exertional chest pain that is relieved by rest or nitrates.

Medical treatment aims to relieve angina and prevent cardiovascular events. Beta blockers and calcium channel antagonists are first-line options for treatment. Short-acting nitrates can be used for symptom relief.

Low-dose aspirin and statins are prescribed to prevent cardiovascular events.