Name: Saliu Halima

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BCH308 Cellular Biochemistry Assignment

**Question**

Describe in details the synthesis of two named neurotransmitters.

**Answer**

1. **Synthesis of Epinephrine**

Epinephrine, also called adrenaline, hormone that is secretes mainly by the medulla of the adrenal glands and that functions primarily to increase cardiac output and that functions primarily to increase cardiac output and to raise glucose levels in the blood. Epinephrine typically is released during acute stress, and its stimulatory effects fortify and prepare an individual for either ‘fight or flight’. Epinephrine is closely related in structure to norepinephrine, differing only in the presence of a methyl group on the nitrogen side chain. In both substances, the amine (nitrogen-containing) group is attached to a catechol group (a benzene ring with two hydroxyl groups) – a structure unique to the catecholamines. Both substances are key stimulatory components of the sympathetic nervous system (part of the autonomic nervous system), hence their pharmacological classification as sympathomimetic agents.

**Synthesis and Production of Epinephrine**

Epinephrine is produced specifically in the adrenal medulla, where the amino acid **tyrosine** is transformed through a series of reactions to norepinephrine. An enzyme known as phenyl ethanolamine N-methyltransferase, which is found in the chromaffin cells of the adrenal medulla, catalyzes the methylation of norepinephrine to epinephrine. In addition to the release of epinephrine from the adrenal glands, small amounts of the hormone are also released from the ends of sympathetic nerves.

Preganglionic fibers of the sympathetic nervous system synapse within the adrenals. Activation of these preganglionic fibers releases acetyl choline, which binds to postjunctional nicotinic receptors in the tissue. This leads to stimulation of norepinephrine(NE) synthesis within adenomedullary cells, but unlike sympathetic neurons, there is an additional enzyme (phenylethanolamine-N-methyltransferase) that adds a methyl group to the NE molecule to form epinephrine. The epinephrine is released into the blood perfusing the glands and carried throughout the body.

**Physiological Actions**

The actions of epinephrine are complex, owing to its stimulatory effects on alpha and beta adrenergic receptors (or adrenoceptors, so named for their reaction to the adrenal hormones), which produce various responses, depending on the specific receptor and the tissue in which it occurs. Hence, epinephrine causes constriction in many networks of minute blood vessels but dilates the blood vessels in the skeletal muscles and the liver. In the heart, it increases the rate and force of contraction, thus increasing the output of blood and raising blood pressure. In the liver, epinephrine stimulates the breakdown of glycogen to glucose, resulting in an increase in glucose levels in the blood. It also acts to increase the level of circulating free fatty acids. The extra amounts of glucose and fatty acids can be used by the body as fuel in times of stress or danger, when increased alertness and exertion are required. The physiological actions of epinephrine are terminated by metabolic breakdown with Catechol-O-methyltransferase (COMT) or monoamine oxidase (MAO), by reuptake into nerve endings, and by diffusion from active sites.

**Clinical Significance**

Purified active epinephrine is obtained from the adrenal glands of domesticated animals or prepared synthetically for clinical use. Epinephrine may be injected into the heart during cardiac arrest to stimulate heart activity. Epinephrine is also used to treat anaphylaxis (acute systemic allergic reaction), which can occur in response to exposure to certain drugs, insect venoms, and foods (e.g. nuts and shellfish). It is also occasionally used in the emergency treatment of asthma, where its relaxation of smooth muscle helps to open the airways in the treatment of glaucoma, where it appears to both decrease the production of aqueous humor and increase its outflow from the eye, thereby lowering intraocular pressure. In turn, certain disease states are associated with abnormalities in epinephrine production and secretion. For example, epinephrine and other catechol amines are secreted in excessive amounts by pheochromocytomas (tumors of the adrenal glands).

1. **Synthesis of GABA (Gamma Aminobutyric Acid)**

It is a neurotransmitter with multiple functions in the central as well as peripheral nervous system. It is the main inhibitory neurotransmitter in brain. It is responsible for decreasing neuronal excitability and taking part in a number of inhibitory nervous signals. GABA deficiency can result in different movement related diseases

**Structure Synthesis and Release of GABA**

GABA is a naturally occurring amino acid that acts as a neurotransmitter in brain and spinal cord. Like other amino acids, it has a carboxylic (-COOH) group and an amino acid group (-NH3). It is a derivative of glutamate, a non-essential amino acid that is abundantly present in the body.

It is synthesized from glutamic acid (glutamate) in the inhibitory neurons. These inhibitory neurons which produce GABA are referred to as GABAergic neurons. The glutamic acid undergoes decarboxylation reaction to form GABA. This reaction is catalyzed by **glutamate decarboxylase enzyme.** the release of GABA occurs by the same mechanism as followed by other neurotransmitters. When a nerve impulse reaches the pre-synaptic neuron, it causes degranulation of the vesicles containing GABA. As a result, GABA is released into the synaptic cleft and is ready to exert its action on both pre-synaptic as well post-synaptic neurons.

**Mechanism of Action**

Once released into the synaptic cleft, GABA performs its action by binding to its receptors and initiating chemical responses. These responses result in decreased neuronal excitability of the neurons. There are two types of GABA receptors present in the neurons;

* GABAA Receptors

It is an ion channel coupled receptor activated by binding to GABA. Upon activation, it causes an increased Cl- influx into the neurons.

* GABAB Receptors

These are G-protein coupled receptors that are activated by GABA. Upon activation, they cause increased upregulation and opening of potassium channels, mediated by secondary messengers. They also inhibit the activity of adenyl cyclase enzyme and are responsible for reduced activity of calcium channels

Activation of either GABAA or GABAB receptors cause increased depolarization of neurons. As a result, their threshold potential is increased. These neurons with increased depolarization have decreased excitability. They don’t respond to the normal neuronal signals. In this way, nerve impulse transmission is inhibited in the pathways involving GABAergic neurons.

**Effects of GABA**

As an inhibitory neurotransmitter, GABA has a number of effects on CNS as well as the peripheral nervous system. It participates in a number of daily life activities such as;

* **Stress relaxation:** GABA plays an important role in relieving anxiety and stress. The most important factor that contributes to stress and anxiety disorders is increased neuronal activity in the brain. GABA inhibits the neuronal activity in the cerebral neurons. In this way, it allows a person to relieve stress and stay away from anxiety.
* **Blood pressure control**: although GABA mainly acts on the CNS, it also has effects on the peripheral nervous system. Studies have shown that GABA can decrease blood pressure. It can do this by decreasing the sympathetic firing.
* **Heart rate**: by decreasing the sympathetic firing, GABA can also decrease the heart rate.
* **Sleep**: sleep is the time when your brain resets. GABA knows how to do this. Having already stated that GABA can decrease the neuronal activity of the cerebrum, it also helps a person sleep earlier. GABA mimetic drugs are used to treat insomnia due to this ability of GABA.
* **Role in brain development:** GABA regulates- proliferation of neuronal cells, migration and differentiation of newly formed cells, elongation of neurites, formation of synapsis. It is also responsible for causing cell cycle rest.
* **Pain:** GABA has an analgesic effect. It can decrease the firing of neurons that carry the pain stimulations from periphery to brain. It can also slow down the nerve impulses in the pain pathway of the brain.
* **Glucagon secretion**: it is secreted by the beta cells of the pancreas and acts on the neighboring cells of the pancreas. It inhibits the alpha cells and prevents glucagon release that would counter the effects produced by insulin.
* **Immune system:** GABA promotes the immune regulatory responses that tend to inhibit the autoimmune diseases. It also regulates the release of inflammatory cytokines.

**Diseases associated with GABA**

Studies have shown that altered GABA signaling is associated with different brain diseases. Some of these diseases are;

* **Attention deficit hyperactivity disorder(ADHD):** It is a disease characterized by hyperactivity, inattention, and impulsivity, it affects a person in his early age. Patients with ADHD lose control of their behavior. Studies have shown that decreased GABA activity is an important factor in the pathogenesis of ADHD.
* **Epilepsy:** Epilepsy has different types. Epilepsy that occurs in children or teens is associated with ionic changes in postsynaptic GABAA receptors. There is decreased expression of GABAA receptors
* **Depression:** GABA plays an important role in controlling the development of the hippocampus neurons’ maturation and migration. The hippocampus is involved in determining the behavior of a person. Drugs that potentiate GABAB receptors have an antidepressant role.
* **Anxiety:** Decreased GABA activity is associated with anxiety. Drugs that potentiate GABAA receptors are used in anxiety disorders.

**Drugs modifying GABA activity**

* Benzodiazepines
* Barbiturates
* Pregabalin

These drugs are used in conditions like insomnia, anxiety disorders, neuropathic pain etc. They are also used as anesthetics.