Chapter 1

Introductory Chapter: Serotonin - The Most Ancient Neurotransmitter, Hormone and Trophic Factor

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Additional information is available at the end of the chapter

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1. Introduction

This book, as its title indicates, is about "Serotonin: a chemical messenger for all living cells", which is not only present in every tissue of human body but also detected in all aerobic organism including plant and bacteria. In humans, serotonin acts as a trophic factor starts soon after conception and is directly related to the production of serotonin by mother's enterochromaffin cells in the gut and its transfer into the platelets in mother's blood. At the same time from a very early stage of gestation, fetus also starts synthesizing its own serotonin in a special group of nuclei of the midbrain. Soon after serotonergic neurons distribute it throughout the brain and body of the fetus in turn increases division, migration and maturation of both central and peripheral tissues.

Serotonin, which is also known as 5-hydroxytryptamine (5-HT), acts both as neurotransmitter and hormone and is mainly found in the brain, bowels and blood platelets. In 1948, Rapport identified a serum agent that affected vascular tone and called it serotonin. Later, in 1950, he identified chemical composition of serotonin and named it 5-hydroxytryptamine. Serotonin, a biogenic amine is produced by the conversion of amino acid tryptophan in the presence of an enzyme tryptophan hydroxylase (TPH) that exists both in brain and bowel. Till now this enzyme is of two types: TPH1 (found in peripheral organs and CNS) and TPH2 (present only in the brain).

Enteroendocrine cells derived 5-HT acts also as a hormone, which perform multiple functions including inhibition of osteoblast proliferation and promotion of hepatic regeneration. The chemical formula of 5-HT is $N_2OC_{10}H_{12}$, such that 15.8970% nitrogen, 9.0793% oxygen, 68.1598% carbon and 6.8638% hydrogen.

2. Effect of serotonin on brain and body

In the central nervous system, serotonin is synthesized by the neurons of the Raphe nuclei from the amino acid tryptophan through a short metabolic pathway that contains two enzymes: tryptophan hydroxylase and amino acid decarboxylase, and is distributed along the length of the brainstem. Serotonin is released from the varicosities along the axon into the extra-neuronal space this provides a larger area for serotonin to activate its receptors that exist on the dendrites, the cell bodies and the presynaptic terminals of the adjacent neurons. Thus serotonin not only stimulates postsynaptic serotonin receptors but also present on the extrasynaptic neurons.

Thus, it is not a surprise to find significant role of serotonin in the modulation of many behavioral and psychotic disorders such as mood, sleep, appetite, vomiting, sexuality, memory, learning, temperature, cardiovascular and endocrine regulation.

Both high and low levels of serotonin have harmful effect. High serotonin levels cause severe toxicity termed as "serotonin syndrome", which can be fatal in some cases, whereas low levels of serotonin have been associated with migraines, bipolar disorders, apathy, fear, feelings of worthlessness, insomnia, fatigue, anxiety and depression. These pathologies may be explained by the fact that 10% of large dorsal raphe nuclei (largest source of serotonin synthesis) are projected to amygdala and other medium raphe nuclei project to caudate, putamen and olfactory bulb. It is important to mention here that serotonin is required for the metabolism of stress hormone.

Scientific evidence confirms that genetic polymorphisms in the enzyme tryptophan hydroxylase in both TPH1 and TPH2 forms can affect the susceptibility to depression and anxiety. Furthermore, ovarian hormones can affect the expression of tryptophan hydroxylase, triggering postnatal depression and premenstrual stress syndrome, and expression of abnormal serotonergic neurons in infants may lead to high possibility of having sudden infant death syndrome (SIDS). Serotonin is also involved in the regeneration of organs such as liver and bone and induces cell division throughout the body.

Large diversity of serotonin receptors creates its pharmacological complexity. There are at least seven types and eight subtypes of serotonin receptors that have been identified in different areas of the body, and they all have diverse effects. Serotonin receptors are activated by psychoactive drugs such as ecstasy (MDMA), LSD, DMT and psilocybin (a substance found in psychedelic mushrooms). A small dose of ecstasy, for example, stimulates a big release of serotonin in the body causing feelings of well-being and comfort but with many side effects.

5-HT receptors (1–7) are mainly second messenger-gated receptors of which only serotonin type-3 receptor is Ligand-gated ion channel and is involved in nausea and emesis as well as a therapeutic target for depression and other mental conditions. 5-HT1 receptor has five subtypes (5-HT1A–1F, no 1E subtype) which are potential site for anxiolytics and antidepressants as these receptors are mainly responsible for regulating emotions and proprioception. Activation of 5-HT1B and 1D receptors cause vasoconstriction and their antagonists are used for the treatment of schizophrenia and migraines and their partial agonist acts as therapeutic targets for anxiety and depression.

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Similarly, 5-HT2 receptor has three subtypes (5-HT2A–2C) and responsible for sleep, pain and motor regulation and are targeted for conditions such as anxiety, migraine and eating disorders. There are certain psychiatric medications that modulate the levels of serotonin in the human body. These drugs are classified into four general categories: (1) monoamine oxidase inhibitors (MAO), (2) tricyclic (TCA) antidepressants, (3) atypical antipsychotics and (4) selective serotonin reuptake inhibitors (SSRIs). SSRIs are prescribed for the treatment of social phobia, anxiety disorders, panic disorders, obsessive-compulsive disorders (OCD), major depression, irritable bowel syndrome (IBS) and eating disorders.

It is vital to know the mechanism of neuronal communication to understand the mode of action of SSRIs. Briefly, two neurons talk to each other by releasing their neurotransmitters in a space (known as synapse) between them. These neurotransmitters travel from presynaptic neurons via synapse to their specific receptors present on the postsynaptic neurons and stimulate them. Once the postsynaptic neurons receive this signal and get activated, these neurotransmitters go back through the transporters present on the presynaptic neurons. SSRIs are the class of drugs that inhibit these serotonin transporter's activities and let serotonin to halt in synapse for a longer period of time. Whereas TCA will let both serotonin and norepinephrine to stay in the gap for extended period of time than normal so both types of postsynaptic neurons can stimulate completely.

As mentioned earlier, all neurotransmitters, especially biogenic amines (serotonin, norepinephrine and dopamine) regulate each other, for example, stimulating 5-HT2 and 5-HT3 receptors by using SSRIs and result in the decrease in levels of dopamine released from the Substantia Nigra, leading to serious mental health problems. Patients on SSRIs or TCA for a longer period of time or in combination with MAOs become very agitated, having tremor and involuntary muscle contraction leading to impaired respiration, increased carbon dioxide pressure and hypoxia.

The role of 5-HT receptors is a topic of intense research, so more therapeutic applications may be discovered in the future. Concisely, role of serotonin in central nervous system is to control appetite, vomiting, sleep, mood, hallucinations and pain perception, and peripherally, responsible for the contraction of vascular and non-vascular smooth, platelet aggregation, increased capillary permeability and modulation of the release of other neurotransmitters.

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