

Serotonin Receptors and Depression

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Although it was known that there was a vasoconstrictive substance in the blood until the 1940s, it was later named 5-HT (serotonin, 5-hydroxytryptamine). The idea that serotonin, which is observed in the brain and intestines, plays a very important role in controlling mood, has been proven to be true in research.^[1] Synthesized from tryptophan amino acid, 5-HT is transported from neuronal cytoplasm to membrane vesicular monoamine transporters (VMAT).^[2] VMAT's (VMAT1, VMAT2) replace two protons per substrate molecule and meet the required energy with the resulting proton gradient.^[3] Since the VMAT2 pump has a higher affinity than VMAT1, it can create more serotonin density in the synaptic range. Again, due to its high affinity, drug groups such as psychostimulants make it easier to connect and inhibit VMAT2.^[4] Serotonin, which is carried with the help of vesicles, is used in our body by converting monoamine oxidase (MAO) metabolism into serotonin metabolite 5-HIAA (5-Hydroxyindoleacetic acid).^[5] Serotonin receptors are G-protein-bound receptors or ligand-gated ion channels located in the central and peripheral nervous system. They are classified as stimulants and inhibitors according to their

ABSTRACT

Serotonin (5-HT, 5-hydroxytryptamine) is an important neurotransmitter, monoamine and hormone secreted from various parts of the body, affecting the central and peripheral nervous system. Tryptophan amino acid is synthesized by the enzyme tryptophan hydroxylase (TPH). Synthesized serotonin is transported from neuronal cytoplasm to membrane through vesicular monoamine transporters (VMATs). VMATs (VMAT1, VMAT2), a member of the SLC18 gene family, meet the energy they need for transport by creating proton gradient with H⁺-ATPase. Effects of secreted serotonin on our body; Although emotion, reproductive behavior, nutrition and sleep pattern control are the control, when serotonin is mentioned, it comes to mind more anxiety and mood changes control or depression. Depression is a condition of not being able to enjoy the situation, not feeling safe, losing empathy and interest in life. This mood disorder; it has been observed that it is caused by a lack of serotonin in the raphe nuclei of the brain or abnormalities in the serotonin transporter (SERT). Brain-induced neurotrophic factor (BDNF) is a nerve growth factor with functions such as controlling synaptic plasticity and increasing neurogenesis. Research has also shown that it has a very important role in the treatment of depression through its relationship with neurotransmitters. In this review, the working mechanism of VMAT pumps, the role of BDNF and serotonin receptors in serotonergic pathways and depression formation were emphasized.

Keywords: Brain-induced neurotrophic factor, depression, raphe nuclei, serotonin, serotonin transporter, tryptophan hydroxylase.

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function.^[6] Receptors and situations that occur in loss of function are mentioned in detail. In addition, serotonin transporter (SERT/Serotonin transporter) in the presynaptic membrane provide removal of serotonin in the synaptic rift.^[5] Inhibiting these transporters in the shortage of serotonin is the most important way to treat depression.^[7] Depression; the expectations heard in the face of an event are negative. All mood disorders, including depression, are characterized by decreased neurogenesis, changes in synaptic structure and synaptic transmission; all of these are

regulated by the brain-derived neurotrophic factor (BDNF), a neurotrophin that performs numerous functions in the adult central nervous system. Much evidence suggests that BDNF is critically reduced in mood disorders and plays an important role in most antidepressant treatments.^[8] Depression can also be seen as a result of adverse changes in serotonin receptors, serotonin transporters, or decreased or increased serotonin levels.^[7] In this review, the factors that cause depression and some ways that may prevent these factors are explained.

TRYPTOPHAN AND SEROTONIN

Tryptophan (Trp) is a non-polar essential amino acid containing an indol ring. It participates in the structure of compounds such as serotonin and melatonin with its indol ring. It is a combination of nicotinic acid and vitamin niacin, with its destruction of the liver.^[8] Niacin is involved in the regulation of the central nervous system, tryptophan, the source of niacin, is also very important for our body. The

formation of niacin in tryptophan deficiency is also unseable, and problems in regulating brain function cause psychological disorders.

Serotonin is an important neurotransmitter secreted from various parts of the body, affecting the central and peripheral nervous system. Serotonin and serotonin receptors are important in many psychiatric and neurological disorders, including brain function and serotonergic system regulation.^[9] Primary targets for 5-HT neurons in the brain; tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRI) as well as psychostimulants and hallucinogenic drugs.^[10]

Serotonin is a biogenic monoamine that is created in two phases and is related to epinephrine, norepinephrine, dopamine, and histamine. The essential amino acid tryptophan is hydroxied by tryptophan hydroxylase to 5-hydroxytryptophan (5-HTP). 5-HTP decarboxylates to form 5-HT in the second step (Figure 1).^[5]

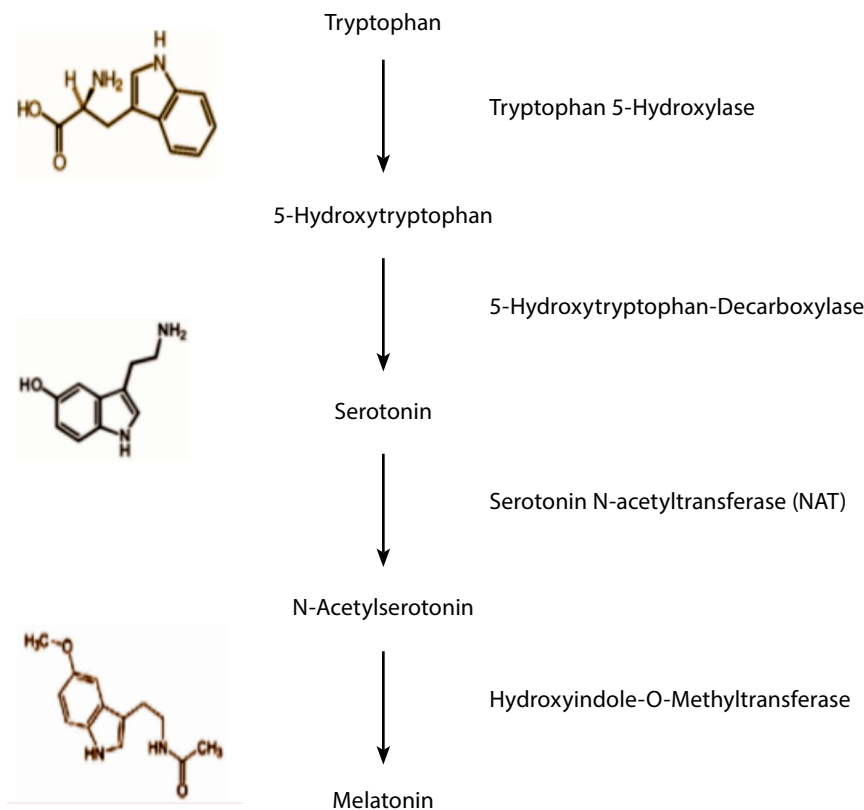


Figure 1. Tryptophan-serotonin-melatonin pathway.

Serotonin is synthesized by the enzyme tryptophan hydroxylase (TPH), which has two isoforms.^[11] Tryptophan hydroxylase 1 (TPH1) from TPH isoforms is considered the speed limiting enzyme of 5-HT synthesis.^[10] Tryptophan hydroxylase 2 (TPH2) is primarily expressed in the neurons of the raphe nuclei of the brain stem and in a subset of neurons in the enteric nervous system (ENS).^[11] Approximately 90-95% of serotonin in the body is found in the periphery and is mostly stored in platelets and enterochromaffin cells (non-neural intestinal cells).^[5] In a study, it was observed that serotonin decreased in the intestines of mice without microbiota. These mice exhibit models of intestinal motility that can be corrected on abnormal ENS, neuroanatomy and microbiota colonization due to 5-HT. The intestinal microbiota plays an important role in the development and maintenance of the serotonergic network within ENS.^[11]

VMAT MECHANISM AND THE TRANSPORT OF SEROTONIN FROM NEURONAL CYTOPLASM

In order for synthesized serotonin to be secreted into the synaptic rift, it must first be transported from neuronal cytoplasm to the membrane. H⁺-linked vesicular monoamine transporter (VMAT) mediates the packaging of monoamine serotonin (including dopamine, norepinephrine and other monoamines such as histamine) from neuronal cytoplasm to presynaptic vesicles. Classical synaptic transmission involves the release of the neurotransmitter from the presynaptic cell into the synaptic rift. Here it interacts with receptors on the postsynaptic cell, leading to signal transmission. Then VMAT's (VMAT1 and VMAT2) remove the neurotransmitter from the cytoplasm and store it in secretion vesicles.^[2] VMAT's meet the energy required for transport with proton gradient created by vesicular H⁺-ATPase, resulting in two-lumen proton exchange.^[12] VMAT's are members of the SLC18 transporter family, which includes the vesicular acetylcholine transporter (VAChT),^[13] both in neurons and neuroendocrine cells.^[14] The main biological function for members of the SLC18 family is the storage and release of neurotransmitters. VAChT transporter acetylcholine; VMAT1 (SLC18A1) and VMAT2 (SLC18A2) carry various types of monoamine neurotransmitters, including dopamine, serotonin and norepinephrine.^[12]

For most monoamines (especially serotonin), the affinity of VMAT2 is higher than VMAT1.^[12] That

is, the density of serotonin in the synaptic range where the VMAT2 pump is located is greater than the VMAT1 pump. Psychostimulants (amphetamines and its derivatives) and TCA group drugs more easily inhibit VMAT2 because of their high affinity. Studies using a genetic rodent model to understand clinical depression in humans suggest that VMAT2 genetic or functional changes may play a role in depression.^[15] In certain sub-regions of the striatum involved in clinical depression, decreased levels of VMAT2, including the nucleus accumbens (NAc) shell, but also decreased in the nucleus, the ventral tegmental area (VTA) and the substantia nigra pars compacta.^[4]

SEROTONIN IN THE CENTRAL SYSTEM

After neuronal storage, serotonin is released into the synaptic rift. It can be connected to postsynaptic serotonin receptors (5-HT receptors) or serotonin autoreceptors in the presynaptic membrane. Binding serotonin to the autoreceptor serves as negative feedback against further release into the synaptic rift. Highly selective SERT, located in the presynaptic membrane, is responsible for removing serotonin in the synaptic slit. When serotonin is transported to the presynaptic neuron, it is recycled into presynaptic vesicles to protect against metabolism. Serotonin to be used is converted to 5-HIAA in cytosol with MAO metabolism. The alternative way for serotonin in the pineal gland (epiphysis cerebri) is the conversion to melatonin.^[5]

RELATIONSHIP BETWEEN SEROTONIN AND DEPRESSION

Depression is a condition in which the cause is not fully known, the person does not enjoy the situation, the environment, does not feel safe and happy, loses empathy and interest in life. In the 1960s, the monoamine hypothesis was established during efforts to develop new antihistamine drugs (aimed at eliminating the effects of histamine at the time of allergy).

The monoamine hypothesis is a hypothesis that seeks to explain the role of monoamine neurotransmitter deficiency in the biological etiology of depression. However, in the researches, the increase in the amount of neurotransmitters with the taking of antidepressants and the failure to adapt the response seen in the clinic as timing required the development of new hypotheses. According to the monoamine receptor hypothesis

developed later; Upregulation or other receptor dysfunctions in postsynaptic receptors due to lack of neurotransmitters, stress or hereditary receptor abnormalities have been identified as the cause of depression. Pathology in receptors has been shown to be caused by a monoamine neurotransmitter defect, receptors themselves or a problem with signal transduction.^[16]

In the biosynthesis of serotonin, aromatic substrates are kept in place by the interactions of enzymes with aromatic amino acid residues, partial dispersion (homogeneous presence of insoluble substances) and induction (altering the shape of the enzyme active center of the substrate). Mutations that reduce substrate binding can lead to a decrease in serotonin production and lead to disorders such as depression.^[17] Serotonergic deficiency can occur on any of several levels. These include decreased precursor compound, impairment of TPH activity, abnormalities in 5-HT oscillation or intake, 5-HT receptor abnormalities or interactions with other neurotransmitters.^[7]

There are also theories suggesting that depression has "serotonergic hyperfunction." Due to the decrease in 5-HT reuptake in platelets of depressed patients, the increase in the amount of serotonin present in the synaptic range leads to an increase in serotonergic neural transmission. In addition, there is an increase in the sensitivity of postsynaptic 5-HT receptors in depressive patients and in the frontal cortex of individuals who die due to suicide, in the number of postsynaptic 5-HT2 and β -adrenergic receptors. The antidepressant effect of tianeptin, a medication that enhances 5-HT reuptake from the serotonin pump and thus reduces the amount of neurotransmitter in the synaptic cleft, indicates that serotonin hypofunction as well as serotonin hyperfunction have a role in the etiology of depression.^[18,19]

SEROTONIN RECEPTORS AND DEPRESSION

The most important factor leading to the development of depression is changes in serotonin receptors. Serotonin receptors can be found in the center or on the periphery of cells, such as neurons or lymphocytes, and they differ depending on whether they are presynaptic or postsynaptic.^[20] Serotonin receptors are divided into seven classes. 5-HT1 and 5-HT5 are inhibitory, but 5-HT2, 5-HT3, 5-HT4, 5-HT6, and 5-HT7 are stimulating.^[21] Just as

each behavior is regulated by multiple serotonin receptors, each serotonin receptor is expressed in multiple brain regions. In this way, it contributes to the modulation of the multiple behavioral processes. For example, anxiety-like behavior is primarily regulated by 5-HT1A, but 5-HT2C receptors regulate not only anxiety, but also reward processing, mobility, appetite and energy balance. This principle explains why drugs targeting a particular serotonin receptor have an effect on multiple behavioral processes.^[22]

Serotonin subtypes that play an important role in depression and related disorders are 5-HT1A-B, 5-HT2A, 5-HT3. 5-HT1 receptors are dense in the dorsal raphe nuclei in the entire human brain cortex, except for the presantral and postcentral gyrus. SSRIs also have anti-bulimic effect by disinhibition in prefrontal roads, antidepressants, basal ganglia with the same effect, antiobsessional, limbic cortex and disinhibition in the hippocampus and disinhibition in the hypothalamic paths.^[23] 5-HT2A and 5-HT2C receptors are members of the super family of 7-transmembrane-spanning (7-TMS) receptors, also known as G-protein-bound receptors. These receptors are found in the brain, especially in the cortico limbic region such as the amygdala, hippocampus, frontal cortex, VTA, nucleus accumbens and hypothalamus. 5-HT 2A is a postsynaptic regulator receptor, usually referred to as 5-HT2. With arousal, it activates transmitters systems in the postsynaptic cell, that is, phosphatidylinositol, the second messenger systems. These allow the production of transducer factors (transcription) that will produce the desired effect within the cell. These receptors store in the membranes and function in vascular contraction (shrinkage), shape change of lymphocytes, head navigation. 5-HT2 receptors are one of the most important receptors considered in the treatment of depression. Antidepressant drugs reduce the density of these receptors.^[23]

BDNF AND DEPRESSION

Brain-derived neurotrophic factor is a growth factor that serves many critical functions within the central nervous system (CNS). It plays a role in processes such as neuronal maturation, synapse formation and synaptic plasticity in the brain.^[24] It has also been shown to increase neurogenesis. For example, intraventricular infusion of BDNF, or Adenoviral-induced BDNF activity, increases the number of neurons in the adult olfactory bulb, striatum, septum and thalamus.^[25-27] BDNF, It is

effective on both presynaptic and postsynaptic response: by increasing the release of presynaptic neurotransmitters, facilitating long-term potency (LTP) industrious activity in schaffer deposits of the hippocampus (learning and memory assurance) in young animals^[28] and increasing the conductivity of NMDA receptors.^[29]

BDNF also plays a role in the development of mood disorders such as depression and treatment in a number of psychiatric disorders, including schizophrenia, intellectual disability and autism.^[30] Environmental stresses such as inactivity that trigger depression also reduce BDNF mRNA,^[31] while physical exercise is associated with reduced depression and increased BDNF mRNA.^[32] Early studies involving BDNF in antidepressant responses have shown that in addition to traditional antidepressant drugs, electroconvulsive therapy increases BDNF and TrkB (Tropomyosin receptor kinase B) mRNA expression in hippocampus and cortical regions over a period similar to the onset of an antidepressant-like response.^[33,34] Exogenous administration of BDNF promotes the functioning and sprouting of serotonergic neurons in adult rat brains^[35] and serotonergic innervation is missing in mice devoid of BDNF.^[36] Therefore, new pharmacological strategies are focused on the potential antidepressant role of BDNF.

Current treatments for depression are thought to mainly act by increasing endogenous monoaminergic (i.e. serotonergic and noradrenergic) synaptic transmission. Recent studies have shown that effective antidepressants increase BDNF mRNA^[37] and protein.

DEPRESSION TREATMENT

Serotonergic stimulation through 5-HT_{2A} receptors reduces the release of dopamine and noradrenaline, while 5-HT_{2A} antagonism increases the release of dopamine and noradrenaline by eliminating this indirect reduction (disinhibition). Numerous laboratory studies have shown increased dopamine and noradrenaline release in the rat prefrontal cortex given 5-HT_{2A} antagonists. The effect of 5-HT_{2A} antagonism on the prefrontal cortex is important for improvement in negative, cognitive and depressive symptoms.^[38]

5-HT_{1A} receptor activity through postsynaptic receptors leads to suppression of serotonergic neurons. 5-HT_{1A} partial agonism (weak effect), observed with atypical antipsychotics (drugs

with high antiserotonergic efficacy), is thought to contribute to anxiolytic and antidepressant effect by filling presynaptic serotonin stores, i.e. increasing serotonin neuronal disinhibition.^[39] Decreased serotonin levels in the synaptic rift cause depression. In order to prevent serotonin reduction, the retrieval system must be inhibited. Some inhibitors that inhibit this system are specific in that they do not inhibit the active intake system on norepinephrine neurons.^[40] Depression can occur in a lack of serotonin or in the excess of norepinephrine. Therefore, the drugs to be used in the treatment process should be in accordance with the mechanism of serotonin-norepinephrine. The most commonly examined specific inhibitor of the serotonin neuron pump is fluoxetine (Lilly 110140). Given fluoxetine or other specific serotonin intake inhibitors, a decrease occurs in the serotonin cycle, and the rate of firing of single neural units in the serotonin-rich raphe region of the brain decreases.^[40]

The first antidepressant drugs, TCA and monoamine oxidase inhibitors (MAOI) were discovered through clinical observations. These first-generation drugs have been shown to be very effective. Because when developing serotonergic or noradrenergic mechanisms, sometimes they can improve both mechanisms. Unfortunately, TCAs have also been found to block histamine, cholinergic and alpha 1-adrenergic receptor regions, resulting in undesirable side effects such as weight gain, dry mouth, constipation, lethargy and dizziness. MAOI, on the other hand, was observed to interact with Tyramine and cause fatal hypertension.^[41] The most commonly prescribed agents are SSRI. SSRI increases serotonergic neurotransmission, but their side effects are also seen.^[42] By increasing extracellular serotonin, they disrupt energy balance and often worsen symptoms during acute treatment.^[21]

However, we can say that BDNF also plays an important role in depression. Over the past decade, several studies have consistently highlighted that BDNF is a key player in antidepressant action. An increase in hippocampal and cortical expression of BDNF mRNA is in line with the antidepressant-like response of traditional antidepressants such as SSRIs. Subsequent studies have shown that the infusion of single-sided BDNF into the ventricles or directly into the hippocampus is sufficient to induce a relatively rapid and continuous antidepressant-like effect.^[24]

DISCUSSION-CONCLUSION

We can say that depression may occur in the excessive decrease in the amount of serotonin and in the excessive increase. 5-HT_{1A} serotonin receptor, suppressor of serotonin release; The 5-HT₂ receptor is a stimulating receptor. The 5-HT_{1A} receptor reduces the amount of serotonin under normal conditions, while the 5-HT₂ receptor increases the amount of serotonin. As a result of the fact that neither of these receptors works evenly, excessive decreases or increases in the amount of serotonin are observed, resulting in depression. In order to treat depression, the answer to whether the cause is serotonin excess or deficiency is very important. Serotonin deficiency may suggest that the 5-HT_{1A} receptor functions with its own agonist, as well as the 5-HT_{2A} receptor may have encountered its own antagonist and its function may have decreased. So a compound of 5-HT_{1A} antagonist or 5-HT₂ agonist can be used in serotonin deficiency. Likewise, MAO metabolism, another cause of serotonin decline, can be inhibited, and serotonin levels can be balanced. ECT or electroconvulsive therapy to increase BDNF and consequently neurotransmitter secretion by passing electric current through the brain is also a key method in depression and similar psychiatric disorders.

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