

A brief analysis of the mechanism of treatment of depression based on the 5-HT hypothesis

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Abstract. Depression is the most common form of depressive disorder and is characterised by significant and persistent depression, usually with a prolonged onset (longer than two weeks) and a tendency for recurrent episodes. In today's rapidly developing society, depression is becoming more prevalent at a younger age and therefore research and development of drugs for depression is urgent, but single-target depression treatments are no longer suitable for today's research due to their high cost and toxic side effects. This paper is therefore based on the 5-hydroxytryptamine receptor hypothesis and analyses the pathogenesis of depression as well as the receptors and their mechanisms of action.

Keywords: 5-ht, depression, hypothesis.

Depression is a typical condition of depressive disorder. It is characterised by significant and persistent depression. Some patients suffer from self-injurious and suicidal behaviour, which may be accompanied by psychotic symptoms such as delusions and hallucinations. In severe cases, depressive malaise may occur, which may be characterised by fixed facial expressions, lack of response to stimuli, little or even no speech, and little or no movement. Depressive episodes are usually characterised by depressed mood, reduced interest and lack of energy. In addition, depression is a mental disorder with a high prevalence and clinical cure rate, but it is also characterised by a low uptake of treatment and a high relapse rate due to a lack of awareness of the disorder, resulting in fewer patients adhering to treatment.

Modern medical research has found that 5-HT, a neurotransmitter responsible for transmitting messages between nerve cells and involved in the regulation of mental, emotional and excitatory conditions in humans, is closely linked to the development of depression.

1. Mechanisms of depression

1.1 The 5-hydroxytryptamine receptor hypothesis

5-Hydroxytryptamine, an indole derivative, is an inhibitory neurotransmitter that, according to modern medical research, acts as a neurotransmitter to produce pleasurable moods and affects almost every aspect of the brain, from regulating mood, energy and memory to shaping outlook on life. Recent research on 5-hydroxytryptamine has shown that without sufficient activity in the 5-hydroxytryptamine receptor, impulses cannot be transmitted and the resulting depression will not be addressed at its source, no matter how much the number of free neurotransmitters is increased. According to the 5-hydroxytryptamine receptor hypothesis, the development of depression is linked in one way or another to multiple receptors for a variety of 5-hydroxytryptamines.

1.2 Mechanism of action of the 5-HT_{1A} receptor

Studies have shown [1] that 5-HT_{1A} receptors are mainly located in the hippocampus and septal nuclei, but also in the frontal cortex. The receptors control the electrical impulses of 5-HT cells and thus regulate the release of 5-HT.

Explanation of the likelihood of 5-HT_{1A} receptors for the development of depression

It can be inferred from the above studies that the development of depression is likely to be related to the hypersensitive upregulation of the 5-HT_{1A} receptor. The 5-HT_{1A} receptor, which is sensitive to 5-HT, is increased by certain physicochemical factors, the 5-HT receptor is increased by the 5-HT_{1A} receptor, and the 5-HT synthesis and release of 5-HT is inhibited by the 5-HT receptor, which decreases the amount of 5-HT in the synaptic gap, resulting in insufficient neurotransmitters to trigger nerve impulses, leading to depression.

1.3 Mechanism of action of the 5-HT_{2A} receptor

5-HT_{2A} receptors are widely distributed in the cortex [2] and subcortex [3] and play an important role in mood, cognition, and memory in humans.

5-HT_{2A} R leads to spontaneous excitation of glutamatergic pyramidal cells by depolarizing the post-synthetic potential and by inhibiting the post-hyperpolarizing current, which also contributes to increased excitability of glutamatergic pyramidal cells [4]. However, excessive amounts of 5-HT_{2A} R may lead to dysregulation of the apical dendritic ion channel, preventing glutamatergic cone cells from returning to a resting potential state, maintaining a hyperactive state, and potentially leading to further psychotic behaviour.

Explanation of the likelihood of 5-HT_{2A} receptors for the development of depression

According to studies, the 5-HT_{1A} receptor shows antagonistic effects with the 5-HT_{2A} receptor and if 5-HT is acting on the hypersensitive upregulated 5-HT_{2A} receptor may lead to the development of depression and anxiety.

Clinical studies have shown that when depressed patients are chronically treated with SSRIs that hypersensitize and downregulate 5-HT_{2A} receptors, an increase in 5-HT levels in the synaptic gap acts to hypersensitize and downregulate 5-HT_{2A}, resulting in significant improvements in depression and anxiety. In addition, hypersensitivity upregulation of the 5-HT₂ class (including 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}) receptors produces depression, anxiety, sleep disturbance and other psychiatric disorders. According to a survey of more than 2,000 depressed and normal subjects, the 5-HT_{2C} receptor density is much higher in depressed subjects than in normal subjects. This in turn supports at a clinical level the influence of 5-HT_{2C} receptors on human mood.

1.4 Analysis of the mechanism of action and biochemical mechanisms of the 5-HT₆ receptor

5-HT₆ receptors are mainly located in the central nervous system, concentrated in the hippocampus, cortex. Studies have shown that 5-HT₆ is mainly expressed in cholinergic neurons [5] and can be involved in regulating the release of a variety of neurotransmitters

It is widely distributed in the hippocampus and therefore has a significant effect on memory. Studies have shown that 5-HT₆ antagonists lead to acetylcholine (ACh) release in both whole/ex vivo experiments [6], and 5-HT₆ agonists increase GABA release in rat cortex, hippocampus and other brain regions and reduce dopamine (DA) and 5-HT efflux, which can be blocked by 5-HT₆ antagonists; about 20% of 5-HT₆ positive neurons are GABAergic neurons, whose ligands may regulate glutamatergic and cholinergic system function by disinhibiting GABAergic neurons [7]. These results suggest that the memory-enhancing effects of 5-HT₆ are at least partially cholinergic-mediated. Not only does 5-HT₆ influence cognitive processes and mood (depression/psychosis) by participating in the regulation of neurotransmitter levels of GABA, Glu, ACh and DA, but it also appears to be involved in motivated behaviour (e.g. eating, addiction, etc.) [8].

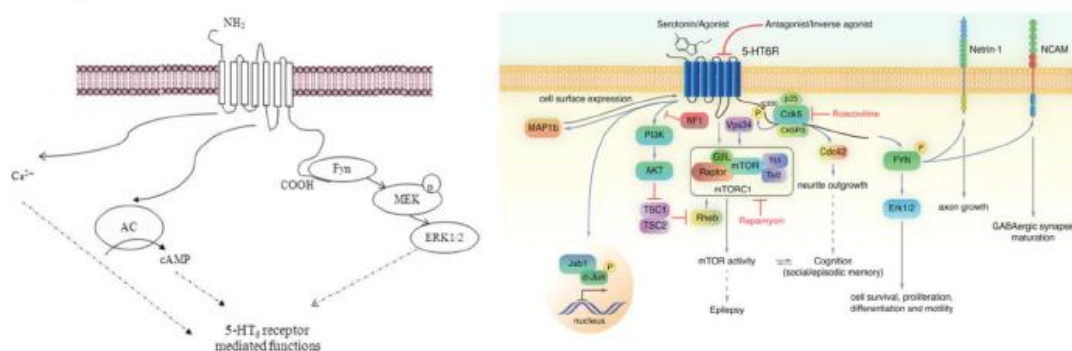


Fig. 1 Schematic diagram of the biochemical mechanism of 5-HT6 receptor function [9]

5-HT6 agonists increase learning memory function for the following possible reasons: 1) 5-HT6 ligands act on other 5-HT receptors [10]; 2) ligands act on different regional receptor populations in the brain, e.g. 5-HT6 agonists act on glutamatergic and cholinergic receptor neurons and antagonists act on GABAergic neurons, all of which can lead to Glu and Ach release and elicit pro-cognitive behaviour [11].

2. 5-HT target database analysis

2.1 Target prediction

After searching, 18 targets of 5-Hydroxytryptamine were found and the number of depression-related targets was 12,978. A genetic comparison of the targets present with depression-related targets yielded 18 targets that may be relevant for the association of 5-ht with depression.

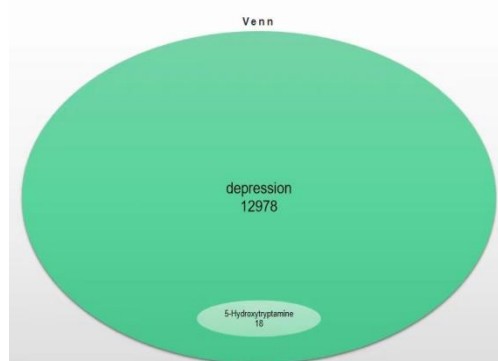


Figure 2. venn diagram of the intersection of 5-ht targets and depression targets

2.2 Biofunctional and pathway enrichment analysis.

The intersecting targets were imported into the database DAVID[14] for GO and KEGG pathway enrichment analysis.

2.2.1 Gene function (GO) analysis of target proteins

To illustrate the role of the targets of 5-ht in gene function, the above screened targets of 5-ht for depression were imported into the DAVID v6.8 database, and the results showed that the total number of biological functions enriched by GO was 12,978, and after setting $P < 0.05$ for screening, the 3 aspects of biological process (BP), molecular function (MF) and cellular component (CC) were derived. The enriched entries were visualized and plotted (see Fig. 3), with 42, 11 and 10 entries in order. The results showed that in terms of BP, biological processes such as chemical synaptic transmission, inorganic cation transport across the membrane and regulation of receptor signalling pathways were involved; in terms of MF, molecular functions such as neurotransmitter-receptor

binding, serotonin binding and ion channel activity were involved; and in terms of CC, cellular components such as cell membrane, cytoplasm and synaptic membrane were involved.

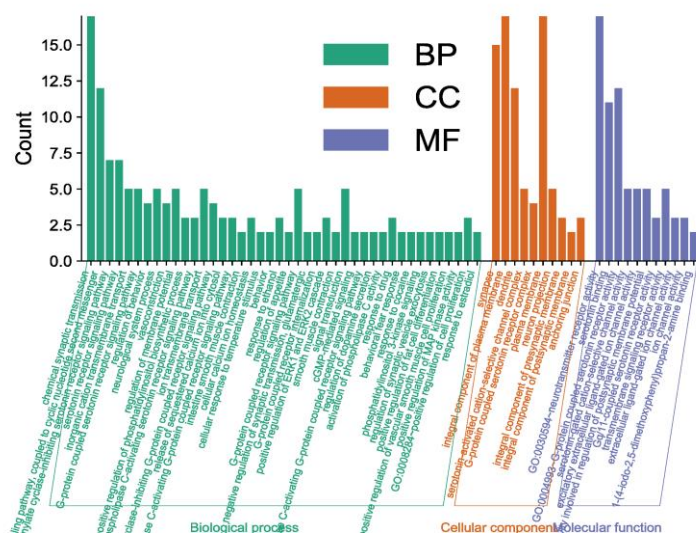


Figure 3. go enrichment analysis graph

2.2.2 Pathway enrichment of target proteins (KEGG) analysis

The KEGG pathway enrichment analysis revealed a total of 18 enriched pathways, and after setting $P < 0.05$ for screening, a total of 7 pathways were obtained, which were plotted in bubble diagrams (Figure 4). 55%), Neuroactive ligand-receptor interaction (12 targets, 66%), cAMP signalling pathway (7 targets, 38%), Calcium signalling pathway (7 targets, 38%), Gap junction (3 targets, 16%), Inflammatory mediator regulation of TRP channels (3 targets, 16%)

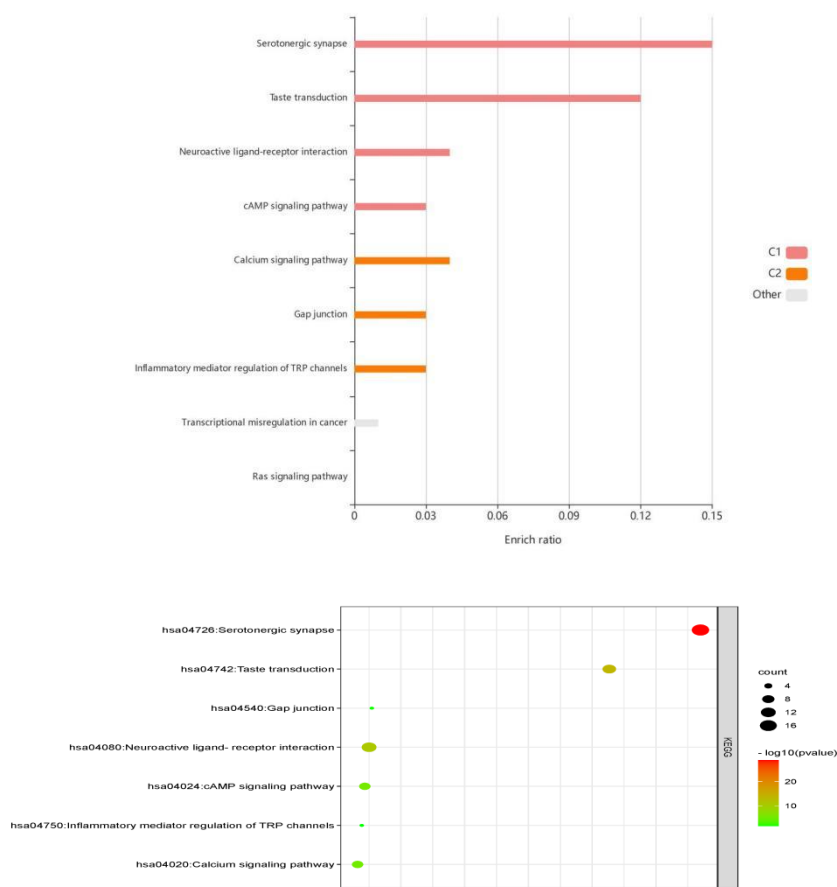


Figure 4. KEGG pathway enrichment analysis

The size of the circles represents the number of genes enriched to this pathway, with a progression from fluorescent colours to red indicating increasingly significant enrichment from larger to smaller p-values. The above results suggest that 5-ht may act primarily by regulating serotonin concentrations in neurotransmitters.

GO enrichment analysis showed that 5-ht treatment of depression mainly involves biological processes such as chemical synaptic transmission, inorganic cation transport across membranes, and regulation of receptor signalling pathways. Neurotransmitters are specific chemicals in chemical synaptic transmission. 5-ht, as an important neurotransmitter in the brain, has complex receptor fractions and extensive synaptic connections between brain regions involved in mood regulation and 5-htergic nerve fibres; at the same time, the balance of the internal environment (e.g. inter-neurotransmitter or neuroendocrine immune network) of depressed patients is disrupted. 5-ht restores the balance of the internal environment of depressed patients by regulating the transport of inorganic ions and receptor 5-ht restores the homeostasis of the internal environment in depressed patients by regulating inorganic ion transport and receptor signalling pathways.

KEGG analysis shows that 5-ht treatment of depression involves pathways primarily associated with serotonin-containing neurosynapses. Serotonin is a chemical signalling molecule that allows nerve cells to communicate with each other and is the most widely studied neurotransmitter in depression. It affects the structure and function of the brain by regulating the proliferation, migration and apoptosis of neural progenitor cells during brain development, influencing the social cognition and emotional processing abilities of individuals, and serotonin plays an important role in the treatment of depression. Serotonin concentrations in the central nervous system are regulated by a variety of enzymes, transporters and receptors, and the rate of serotonin synthesis is affected. When intra-synaptic serotonin is reduced, serotonin transporters can reintake serotonin from the synaptic gap into presynaptic cells.

2.3 Construction of target protein interaction (PPI) networks

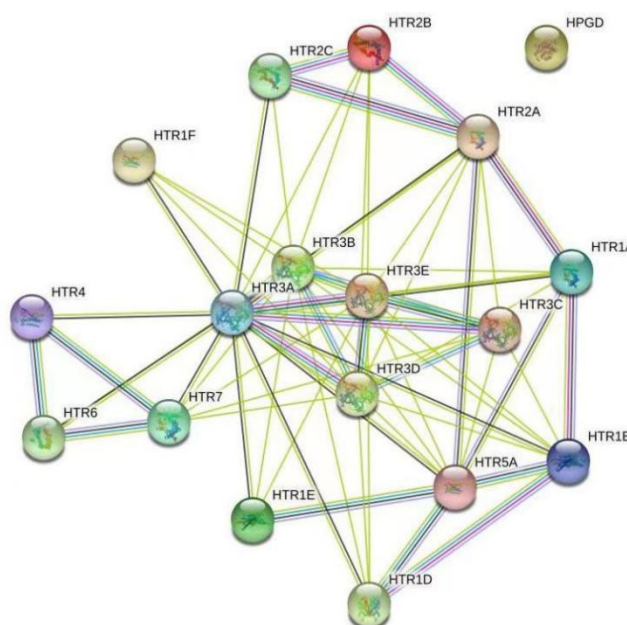


Figure 5. PPI diagram of potential targets for association analysis of 5-ht and depression production

The 5-ht and depression targets were uploaded sequentially to the Uniprot database [13] for target gene normalisation and the common targets were uploaded to STRING to map the PPI network.

A PPI network was constructed on the STRING platform with the species set to "Homo sapiens", the minimum interaction threshold set to "Medium confidence" 0.4, and the other parameters kept at the default settings. The default setting was set to "Homo sapiens", the minimum interaction threshold

was set to "Medium confidence" 0.4, and the other parameters were kept as default. As shown in Figure 4, the core common targets contained 17 points and 68 edges.

3. Mechanisms and associations of 5-HT in the clinical treatment of depression

Currently, the mechanism of action of drugs used clinically to treat depression is mostly through the enhancement of neurotransmitters such as 5-hydroxytryptamine (5-HT) or norepinephrine (NE or NA, Norepinephrine), for example, fluvoxamine [15] is effective in improving depressive symptoms in adolescents, and duloxetine hydrochloride [16] is effective in treating menopausal depression. Since the 1980s, the use of classic tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) has declined and selective serotonin reuptake inhibitors (SSRIs) have come into clinical use with good clinical efficacy [17].

3.1 5-HT

5-HT, a factor that regulates emotional behaviour, is mainly found in the medulla oblongata, pontine and midbrain septal nuclei of the central nervous system. 5-HT receptors contain a variety of subtypes, all of which are located at different effector sites and can play a mediating role. [18]. For example, the 5-HT_{2A} receptor mediates its action through the Gq protein before activating phospholipase C. The 5-HT_{2C} receptor generally uses the activation of the Gq/11 protein to act on the corresponding downstream intracellular effector molecules [19]. Currently, the International Society of Pharmacology classifies 5-HT receptors into seven types (5-HT₁~7). Among them, the 5-HT receptors that are relevant for the treatment of depression are 5-HT₁, 5-HT₂, 5-HT₆ and 5-HT₇, of which the 5-HT₃ receptor also achieves antidepressant efficacy through its own properties. Numerous studies [20, 21] have previously demonstrated that abnormal levels of 5-HT and its metabolites cause a decrease in the amount of 5-HT, which leads to the onset of depression.

In the Wistar-Kyoto (WKY) rat experiment [22], a 30% reduction in 5-HT levels in the dorsal septal nucleus was observed in rats with depressive behaviour compared to normal rats, while no change in 5-HT was observed in the prefrontal cortex [23].

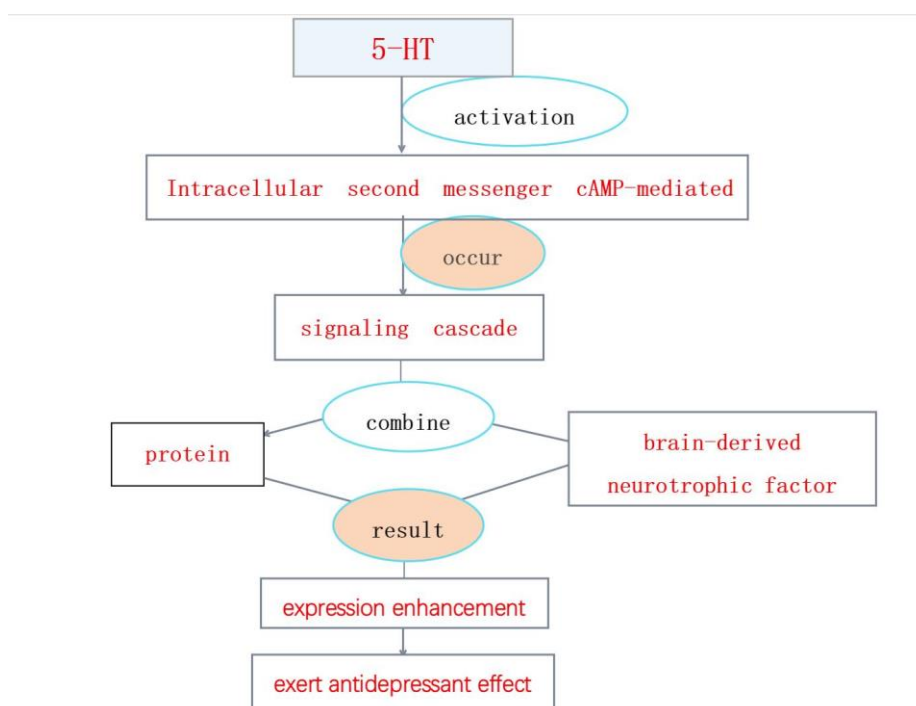


Figure 6. Mechanism of action in clinical trials of 5-HT

3.2 5-HT receptors with therapeutic effects against depression

3.2.1 Clinical applications of 5-HT_{1A} receptors in the treatment of depression.

The 5-HT_{1A} receptor, the first high-affinity and fully sequenced 5-HT receptor, has a similar distribution pattern across species. In contrast, the rat, which is 89% homologous to the human receptor, has 422 amino acids of 5-HT_{1A} with the typical seven tertiary structures [24].

YL0919, a 5-HT_{1A} receptor partial agonist, exhibits antidepressant-anxiety effects behaviourally [25]. The study [26] emphasised that decisive for stress adaptation and antidepressant efficacy is the high expression of 5-HT_{1A} autoreceptors. Richardson-Jones et al. observed that genetic polymorphisms in the promoter region of the human 5-HT_{1A} receptor increased the risk of depression and decreased treatment response [27].

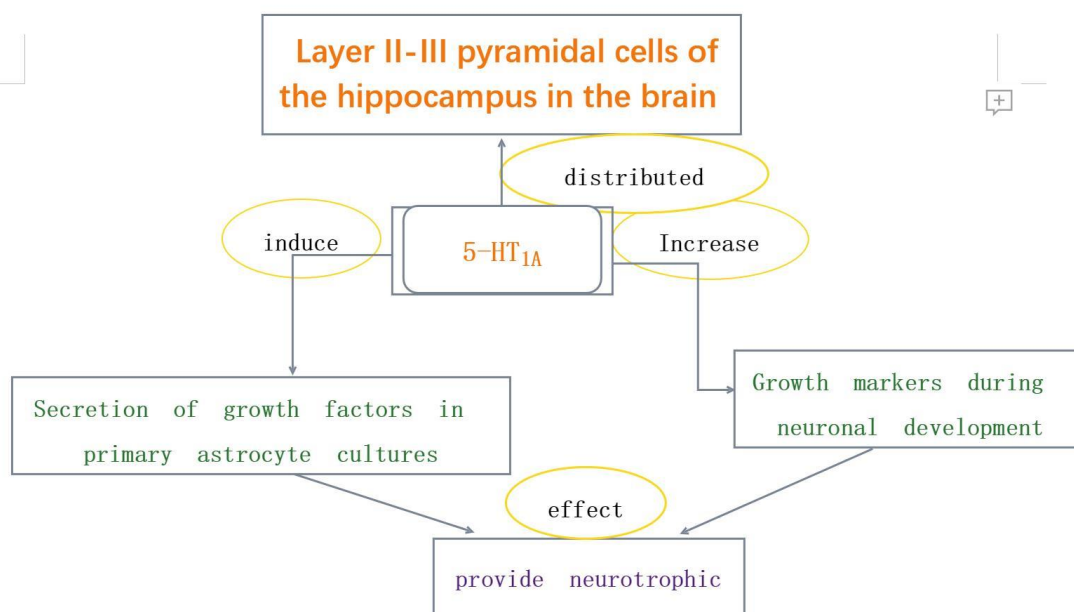


Figure 7. Role of 5-HT_{1A} in clinical trials

The 5-HT_{2A} receptor, usually via the Gq/11 protein[19], activates PLC (phospholipase C), thereby increasing intracellular calcium ion concentrations. Gq protein is an isoform of a heterotrimer of G proteins and PLC is a downstream intracellular effector molecule. 5-HT receptors in the postsynaptic membrane, when agitated, may cause abnormal behavioural activity such as depression, anxiety and insomnia in humans. 5-HT reuptake inhibitors (SSRIs) and lithium carbonate act: inhibiting the release of NE and DA (dopamine) dependent on calcium ions in nerve endings and promoting the synthesis and release of 5-HT to further achieve antidepressant therapeutic effects[28].

The existing study found that the T102C polymorphism of 5-HT_{2A} was selected for experimentation using a typing technique based on the Yasubiro Inayamo method [29] with minor modifications and concluded that there is likely to be an effective effect of the 5-HT_{2A} receptor gene on vulnerability to refractory depression [30].

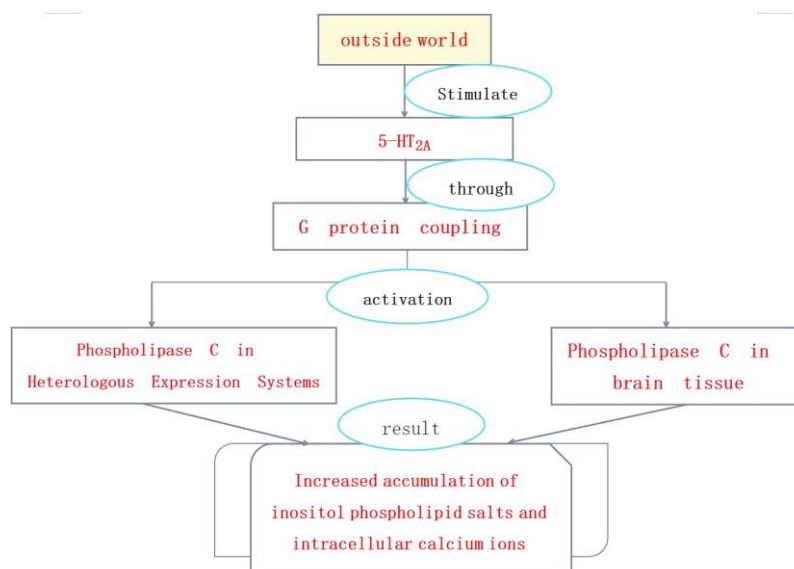


Figure 8. Mechanistic processes of 5-HT2A in the treatment of depression

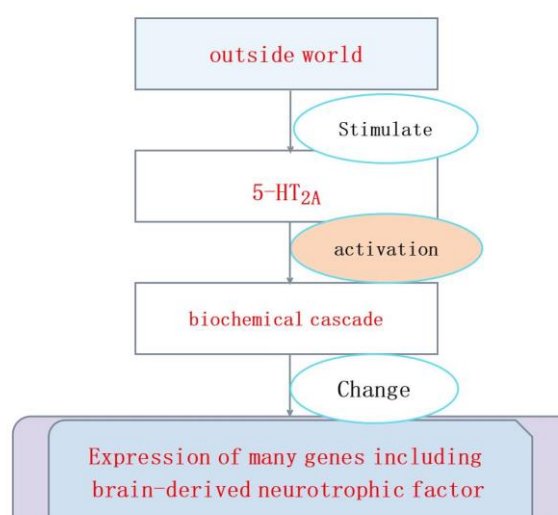


Figure 9. Content change of 5-HT2A in response to external stimuli

The 5-HT2C receptor gene, which shares the same signaling pathway as the 5-HT2A receptor, is located at the q24 region of the human X chromosome [24] and contains three introns, five polymorphic sites in the promoter region, a coding region approximately 1.4 kb long, and four single nucleotide mutations (sSNPs): -997G/A, -759C/T, -697G/C, -1165G/A [31].

By conducting a comparative study between depressed and normal individuals, Lerer et al. found that the serine (N-terminal of the extracellular domain) of the 5-HT2C receptor was replaced by cysteine in depressed individuals at levels far exceeding those of normal individuals [18].

Gene microarray studies have reported that 5-HT2C gene expression is significantly higher in the brains of rats with anger/depressed mood responses compared to normal rats. Available studies suggest that this gene is associated with anxiety, irritability, mania and depression [32].

Currently, it is used in clinical applications to regulate mood and treat depression by antagonizing 5-HT2C receptors, reducing differential 5-HT2C gene expression, and inhibiting the release of dopamine and norepinephrine [33]. A 5-HT2C receptor antagonist, ZY-1408, has shown significant reversal of depressive behaviour in a rat model of chronic stress. Microdialysis results have mentioned that the extracellular concentrations of NE and 5-HT in the hippocampus of rats were significantly increased with ZY-1408 [25].

3.2.2 5-HT₃

The central nervous system, 5-HT₃, is also involved in the pathology of anxiety and depression. If 5-HT₃ is dysfunctional in the hippocampus, it may cause a range of negative emotions such as anxiety, depression and insomnia. 5-HT₃ is the only ligand-gated ion channel receptor in the 5-HT receptor family and is mainly found in the amygdala, hippocampus, dorsal vagal area of the brain and cerebral cortex [34, 35].

Activation of the 5-HT₃ class of receptors is mediated by Na⁺, K⁺ and Ca²⁺, resulting in rapid depolarization of neurons in pre- and postsynaptic cells. [32] The concentration of calcium ions present in the cytoplasm will increase rapidly, thereby affecting the release of neurotransmitters and neuropeptides. It has been shown that 5-HT_{3B} receptor protein levels are increased in the hippocampus and hypothalamus of rats, a model of depression. 5-HT_{3RA} (a 5-HT receptor antagonist) produces antidepressant-like effects by inhibiting the binding of 5-HT to 5-HT₃ receptors at the postsynapse and increasing the utilization of 5-HT₂, 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors. This process may be accomplished by modulating the ion permeability of 5-HT receptors [25].

3.2.3 5-HT₆, 5-HT₇

In clinical application, the 5-HT₆ receptor, as a new targeting mechanism, may be involved in the anxiolytic-depressive mechanism after partial agonism of the 5-HT_{1A} receptor. EMD386088 (5-HT₆ receptor partial agonist) was administered intraperitoneally to forced swimming and olfactory bulb-removed rats for acute and chronic depression, and the results showed that EMD386088 produced antidepressant-like activity after direct action on the 5-HT₆ receptor. [32]

5-HT₇ receptors are mainly located in cortical and limbic brain regions. In clinical practice, a 5-HT₇ receptor antagonist, lurasidone, is often used in combination with a 5-HT₇ receptor antagonist [25] for optimal targeting of 5-HT receptors in the treatment of depression.

The 5-HT₆ and 5-HT₇ receptors both produce a similar response to 5-HT₁ by stimulating G_s, activating AC (adenylate cyclase) and causing cAMP (cyclic adenosine monophosphate) to form [36], which exhibits anxiolytic effects behaviourally.

4. Summary

Modern medicine has never ceased to study the disorders of depressive disorders. It is known from the previous analysis that the pathogenesis and mechanism of depression is indeed linked to 5-HT receptors, in particular the 5-HT_{2C} receptor.

The database analysis of 5-HT, after genetic comparison, predicts that 5-HT may be relevant targets for depression, and after biological function and pathway enrichment analysis, it is known that in terms of BP, it involves chemical synaptic transmission, inorganic cation transport across the membrane, receptor signalling pathway regulation and other biological processes; in terms of MF, it involves neurotransmitter-receptor binding, serotonin binding, ion channel activity and other molecular functions; in terms of CC, it involves cell membrane, cytoplasm, synaptic membrane and other cellular components. The MF aspect involves molecular functions such as neurotransmitter-receptor binding, serotonin binding and ion channel activity; the CC aspect involves cellular components such as cell membrane, cytoplasm and synaptic membrane. It was also possible to determine that 5-HT may act mainly through the regulation of the cAMP signalling pathway and the calcium signalling pathway. Finally, after the construction of a target protein interaction (PPI) network, it was possible to identify a core common target between 5-HT and depression containing a total of 17 points and 68 edges. After analysing the mechanisms of 5-HT in the clinical treatment of depression, it was concluded that 5-HT_{1A} is at risk of depression and reduces treatment response. 5-HT_{2A} receptor gene is likely to have an effective effect on the vulnerability to refractory depression. Receptor antagonism of 5-HT_{2c} has also been shown to modulate mood and treat depression. Antidepressant effects can be produced by modulating the ion permeability of the 5-HT₃ receptor. 5-HT₆ and 5-HT₇ receptors both produce responses similar to those of 5-HT.

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