Recent advances in studies of 5-HT autoreceptors and related transporters

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Abstract. 5-hydroxytryptamine (5-HT) is closely related to emotion regulation and nervous system diseases. Transporters that are related to 5-HT play an essential role in mediating reuptake and clearance of 5-HT. In the central nervous system, 5-HT has a lot of types and subtypes of autoreceptors. The production of 5-HT transporters (SERT) has a certain correlation with the occurrence of mental diseases. The generation can play a role in both the regulation of signal transmission and 5-HT uptake expression and the research of related mental diseases treatment.

Keywords: 5-HT; 5-HT related transporters; 5-HT autoreceptors; selective serotonin reuptake inhibitor; mental diseases.

1. Introduction

In recent years, the increasing and younger tendency of mental disorders has been attracted highly at home and abroad. A variety of mental diseases are closely related to the content of 5-HT, such as depression, anxiety, bipolar disorders, post-traumatic stress syndrome and so on (Cen et al., 2015). A large number of related studies have indicated that the dysfunction of 5-HT is a universally recognized pathogenesis.

5-HT is a type of essential monoamine neurotransmitter, since it was first found in serum, it is also known as serotonin, which is highly conserved chemical that can transmit the nerve signals and widely present in vertebrates and invertebrates. 5-HT mainly participate in the regulation of significant physiological processes such as emotion, cognition and sleep etc (Serretti et al., 2006). 5-HT can play a role in both the central and peripheral nervous systems. In central nervous system, 5-HT in the synaptic cleft can mainly complete the above physiological regulation process. 5-HT binds to the related receptors in post synapse to initiate a cascade reaction through signal conduction and then rapidly dissociates. In the peripheral nervous system, researches indicate that there are nearly 98% of 5-HT in the body existing in the periphery and play an important role in the regulation of vascular contraction and relaxation, the motility of gastrointestinal, the cell proliferation, apoptosis and platelet aggregation (Min & Jihua, 2013).

A large number of studies have proved that the occurrence of multiple mental disorders is closely related to the content of 5-HT. There is the further elaboration of the 5-HT autoreceptors and related transporters as follows.

2. Literature Review

2.1. The recent advances in studies of 5-HT autoreceptors

2.1.1 5-HT autoreceptors in the central nervous system

It is well known that 5-HT autoreceptors belong to G protein-coupled receptors. Up to now, there are 7 subtypes of 5-HT receptors found in the central nervous system, which are 5-HT1-7 receptors. At the same time, these receptors contain multiple different subtypes, such as 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2C receptors and so on. The complex 5-HT autoreceptors family induce the difference of action pathway and mechanisms because of the subtypes and distribution (Dong & Rui, 2012; Xiaofei
et al., 2002). There is a detailed introduction of the action mechanism and function of each receptor, and its subtypes as follows.

2.1.1.1 5-HT$_{1A}$ autoreceptor  
5-HT$_{1A}$ autoreceptor is a G$_{i/o}$ protein-coupled receptor (Dong & Rui, 2012), which is mainly distributed in the presynaptic and postsynaptic membrane of neurons in the hippocampus, raphe nucleus group and frontal cortex (Dong & Rui, 2012; Xiaofei et al., 2002). 5-HT$_{1A}$ autoreceptor can couple with G$_i$ protein to control the electrical signal transmission of cells and inhibit the activity of adenylyl cyclase in order to open the potassium ion channel on the cell membrane (Blattner et al., 2019). Or it can couple with G$_o$ protein to close the calcium channel (Blattner et al., 2019). The above 2 coupling pathways with G protein will decrease the level of cAMP so that the activation of 5-HT$_{1A}$ receptors will reduce the effective expression of 5-HT and low concentration of 5-HT may lead to the generations of depression (Blattner et al., 2019; Dong & Rui, 2012). It has been hypothesized that the occurrence and development of depression is related to the hypersensitivity of 5-HT$_{1A}$ receptor in both presynaptic and postsynaptic membranes, which can be countered by selective serotonin reuptake inhibitor (SSRI) to increase the content of 5-HT in synaptic cleft to achieve the purpose of depression treatment (Dong & Rui, 2012).

2.1.1.2 5-HT$_{1B}$ autoreceptor  
5-HT$_{1B}$ autoreceptor is a G$_i$ protein-coupled receptor, which is mainly distributed in the substantia nigra and globus pallidus of the central nervous system. Since it is distributed on 5-HT neurons, it is known as 5-HT$_{1B}$ autoreceptor (Xiaofei et al., 2002). Researches at home and abroad have shown that 5-HT$_{1B}$ autoreceptor can fine-regulate SERT and both of them are highly expressed in the CA3 subregion of hippocampus (Daws et al., 2000; Montanez et al., 2014; Zhu et al., 2007). 5-HT$_{1B}$ can regulate the concentration of 5-HT in the intercellular synaptic cleft by coupling with G$_i$ protein and regulating the signal conduction.

2.1.1.3 5-HT$_{2}$ receptor  
5-HT$_{2}$ receptor is G$_q$ protein-coupled receptor and mainly distributed in the choroid plexus and hippocampus (Blattner et al., 2019). 5-HT$_{2}$ receptor can accelerate the hydrolysis of phosphatidylinositol by coupling with G$_q$ protein (Xiaofei et al., 2002). After the activation of receptors, it can promote the uptake and expression of 5-HT through the electrical signal transmission, so as to excite the cerebral cortex.

The gene of 5-HT$_{2}$ receptor has structural diversity, which leads to the phenomenon of the substitution of amino acids in the amino acid sequence. The structural change can lead to the diversity of 5-HT$_{2}$ receptors. Furthermore, it can participate in the pathogenesis of unidirectional affective disorder (Xiaofei et al., 2002).

2.1.1.4 5-HT$_{6}$ receptor  
5-HT$_{6}$ receptor is G$_s$ protein-coupled receptor and mainly distributed in striatum, nucleus accumbens and cortex (Dong & Rui, 2012; Xiaofei et al., 2002). 5-HT$_{6}$ receptor can activate the adenylyl cyclase and increase the expression level of 5-HT to excite the neurons through coupling with G$_s$ protein.

Both the agonists and antagonists of 5-HT$_{6}$ receptor have a strong affinity with the receptor, which can bind with receptor and may have antidepressant effects (Dong & Rui, 2012).

2.1.1.5 5-HT$_{7}$ receptor  
5-HT$_{7}$ receptor is G$_s$ protein-coupled receptor and mainly distributed in the thalamus, hypothalamus, brain stem, hippocampus and amygdala (Dong & Rui, 2012; Xiaofei et al., 2002). 5-HT$_{7}$ receptor activates the adenylyl cyclase by coupling with G$_s$ protein (Xiaofei et al., 2002). Furthermore, it can increase the level of 5-HT and excite the neurons.
Researches from all over the world indicate that the antagonists of 5-HT7 receptor can have the role of antidepressant effects, such as amisulpride, SB-269970, imipramine and lurasidone (Dong & Rui, 2012).

3. Recent advances in studies of 5-HT related transporters

3.1. 5-HT transporters (SERT)

Serotonin transporter (SERT) is a key regulator of 5-HT transportation and widely distributed in the limbic system of the brain, the membrane of chromaffin in the gastrointestinal tract, mast cells and the presynaptic membrane of serotonergic nerves (Zhu et al., 2007). It is a Na+/Cl− dependent transporter and mainly located on the neuronal cell membrane. It can mediate and reuptake 5-HT from the synaptic cleft into the presynaptic membrane to regulate the concentration and activity of 5-HT in the synaptic cleft and change the amount of 5-HT received by postsynaptic receptors and the duration of signal transmission. Furthermore, it regulates 5-HT nerve electrical impulses and a series of physiological processes to prevent the formation and accumulation of high 5-HT concentration in the synaptic cleft, which leads to the excitation of sympathetic preganglionic fibres and the inhibition of parasympathetic preganglionic fibres due to the large number of inhibitory neurotransmitters (Min & Jihua, 2013).

In the CA3 subregion of hippocampus, the antagonists of 5-HT1B autoreceptors requires the interaction of both 5-HT1B autoreceptors and SERT to inhibit the concentration of 5-HT. At the same time, experiments have shown that there is a correlation between 5-HT1B autoreceptors and SERT (Daws et al., 2000).

3.2. Dopamine transporter (DAT)

Some researches show that SERT belongs to the monoamine transporter gene family and has a high homology of amino acid sequence with DAT (Dong-Fen et al., 2011). DAT has the similar characteristics with SERT, which can uptake and release 5-HT and may compensate SERT by the effect of SSRIs or the mechanism of 5-HT regulation by the transporter itself (Daws, 2009).

The advance studies indicate that most antagonists of DA receptors cannot well regulate the depression that induced by DA regulation. However, antagonists of 5-HT1B autoreceptors can largely weaken or even block the induction of DA (Daws, 2009). It can be seen that most activation and application of exogenous DA require the mediated regulation of 5-HT1B autoreceptors. And the synergistic effect between 5-HT1B autoreceptors and DA receptors has a greater impact on the activation extent of DA than that of DA receptors alone (Daws, 2009).

3.3. Organic cation transporters

Previous studies on 5-HT transporters have focused on the uptake 1 family of monoamine transporters with high affinity with Na+/Cl−, such as SERT and DAT (Boxberger et al., 2014). Recent studies have shown that the uptake 2 family of organic cation transporters that express low affinity to the brain can also influence the uptake and expression of 5-HT, such as OCT (Koepsell, 2021).

Daws’ s research indicates that monoamine neurotransmitters have a large difference about affinity between the synaptic cleft and the surrounding environment and the monoamine neurotransmitters that close to the synapse have a large Km value and a small affinity, which means that the monoamine neurotransmitter transporters with low affinity are required to effectively remove neurotransmitters after nerve excitation (Daws, 2009). The synergistic action of neurotransmitter transporters with different affinity can precisely regulate the concentration of 5-HT so that transporters with low-affinity can regulate the reuptake of 5-HT (Daws, 2009).

3.3.1 Organic cation transporter (OCT1)

In the central nervous system, OCT1 is mainly distributed in the blood-brain barrier. In the peripheral nervous system, OCT1 is expressed in the liver, kidney and intestine. And it can have the
highest expression in the liver, where it mainly transports the exogenous substances to the liver for metabolism. Studies have indicated that OCT1 in the liver plays a role in the elimination of 5-HT in the liver (Boxberger et al., 2014). Due to the decreased expression level of OCT1 transporter in the liver, the reduction of 5-HT uptake will lead to the increase of 5-HT in the blood circulation (Ying et al., 2022).

3.3.2 Organic cation transporter (OCT2)

OCT2 is mainly distributed in the blood-brain barrier, cortex and hippocampus (Lin et al., 2010). As a member of the uptake 2 monoamine transporter family, OCT2 is abundant in monoaminergic neurons in parts of its distribution areas (Gasser & Lowry, 2018; Matsui et al., 2016; Sugiyama et al., 2019). Through clearing 5-HT, DA and NE in the synaptic cleft, the level of monoamine neurotransmitters in the brain can be regulated. In the peripheral nervous system, OCT2 is mainly distributed in the kidney, where it is excreted by transporting substrates to the kidney (Otsuka et al., 2005).

3.3.3 Organic cation transporter (OCT3)

In contrast to OCT1 and OCT2, OCT3 is more widely distributed in the brain. Some researches have shown that OCT participates in the transportation of endogenous monoamine neurotransmitters, such as endogenous 5-HT, NE and DA (Gasser, 2019). OCT3 has the characteristics of high capacity, bidirectional transport and low affinity (Burke & Alvarez, 2022; Xiaonan et al., 2021). And it plays an essential role in clearing 5-HT in the synaptic cleft and may be a new drug target for the treatment of mental disorders.

3.4 Plasma membrane monoamine transporter (PMAT)

PMAT, a major member of the uptake 2 family, has the higher expression in the brain than other monoamine transporters. Moreover, the transport and clearance ability of PMAT to 5-HT is equivalent to that of SERT with high affinity to transport 5-HT (Parker et al., 2009). PMAT may also serve as a new drug target for the treatment of depression.

4. The relationship between 5-HT autoreceptors and transporters

Some researches have indicated that the combination of the antagonists of 5-HT1A receptors and SSRIs can significantly increase the concentration of 5-HT in the synaptic cleft and greatly enhance the antidepressant effect (Shi-xing et al., 2020). The series of processes of inhibiting the action of 5-HT1B autoreceptor, reducing the reuptake of 5-HT mediated by SERT and clear the 5-HT in the synaptic cleft, can reduce the expression of 5-HT and enhance the effect of SSRIs, increase the concentration and active expression level of 5-HT in the synaptic cleft so that realize the action of antidepressants (Daws et al., 1999). However, the regulatory relationship between 5-HT autoreceptors and transporters is still unclear. Therefore, it is urgent to study the relationship between them to provide new drug targets for the development of antidepressant drugs, which has essential theoretical significance and clinical application prospects.

5. Summary

5-HT is an essential monoamine inhibitory neurotransmitter with key roles in both central and peripheral nervous systems. There are 7 different kinds of 5-HT autoreceptors in the central nervous system. Each receptor and its corresponding receptors subtypes play different roles in the nervous system of body due to the different types of G protein-coupled receptors and different regions of distribution. SERT, which is a member of the Na+/Cl− dependent monoamine neurotransmitter transporter family, has a high homology of amino acid sequence with DA and DA can cooperate with 5-HT autoreceptors and SERT to regulate the 5-HT and DA expression level in the synaptic cleft in vivo. At the same time, organic cation transporters (OCTs) and plasma membrane monoamine
transporter (PMAT), which are as low-affinity transporters, can cooperate with high-affinity transporters to regulate the level of neurotransmitters in the synaptic cleft to change the signal transmission of presynaptic receptors.

5-HT autoreceptors can regulate SERT, inhibit the electrical signal transmission of 5-HT neurons to regulate the reuptake of 5-HT. The above action mechanism provides theoretical ideas for the pathogenesis, treatment and new drug development for SERT-related diseases. It is expected to be a new drug target and new pathway for the treatment of mental disorders.

References


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