

## REVIEW ARTICLE

# 5-HT<sub>3</sub> Receptors: A Potential Therapeutic Target for Epilepsy

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**Abstract: Background:** Epilepsy is a syndrome of brain dysfunction caused by spontaneous, abnormal discharge. Many anti-epileptic drugs have developed in past decades. 5-HT is an important neurotransmitter in the central and peripheral nervous system of the human body which is involved in a number of physiological activities, such as sensation, movement, and behavior. 5-HT subtype have been divided into seven sub-groups from 5-HT<sub>1</sub> to 5HT<sub>7</sub>. However, the role of 5-HT<sub>3</sub> receptor on epilepsy is unclear. Therefore, in this article, the possible role of 5-HT<sub>3</sub> receptor on epilepsy was systemically reviewed.

**Methods:** Data were collected from Web of Science, Medline, Pubmed, Scopus, through searching of these keywords: "5-HT<sub>3</sub>" and "epilepsy".

**Results:** An increasing number of studies have shown that the activation of the 5-HT<sub>3</sub> receptor can inhibit epileptic seizures, while inhibition of the 5-HT<sub>3</sub> receptor can promote spike waves.

**Conclusion:** In this review, we discuss the relationship between the 5HT<sub>3</sub> receptor and epilepsy; this review may provide a new insight for clinical application of epilepsy treatment.

**Keywords:** 5-HT<sub>3</sub> receptor, epilepsy, antagonists, Neuron, GABA, NMDA.

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## 1. INTRODUCTION

Epilepsy is a chronic disorder of the brain caused by sudden abnormal discharge of neurons. It is characterized by persistent changes in the brain that can produce seizures. To date, the disease affects more than 60 million people worldwide [1], making one of the most common neurological disease across the globe. The risk factors for epilepsy include changes in age and geographical location, as well as congenital, developmental, and hereditary factors. Epilepsy typically emerges in childhood, adolescence, or early adulthood. It is the second most common diseases in the nervous system [2]. According to an epidemiological survey, the general population prevalence rate of epilepsy is five per thousand to seven per thousand yearly. There are many causes of epilepsy, though the fundamental reason is understood to be abnormal synchronous discharge secondary to the neural network. Epilepsy is caused by abnormal ion conduction or other changes in neural membrane, or excitatory and inhibitory imbalance [3]. Studies have also indicated a number of complications that can arise at any time during the progression of epilepsy [4].

Countless researchers have proposed a wide variety of treatment for epilepsy, including traditional drug therapy

having gradually extended to cell transplantation, nerve stimulation, gene therapy, and other treatments. As of now, there is no cure, surgery is possible, but introduces a great deal of risk [5]. However, present antiepileptic drugs provide only partial control of seizures [6]. Existed treatments methods are mainly based on managing symptoms that do not affect the underlying disease process, and are often accompanied by severe side effects. Arguably, the ineffectiveness of these treatments mainly is due to the lack of identified target [7]. Frequent and long-term seizures, and subsequently a series of psychological changes not only impact quality of life in epileptic patients, but place a burden upon his or her family and community. In this review, we will focus on further exploration of the pathogenesis of epilepsy in terms of identifying novel drugs and therapeutic targets.

In 1957, Bonnycastle, *et al.* first asserted that there is a relationship between 5-HT and epilepsy inhibition due to the fact that many anti-epileptic drugs increase the concentration of 5-HT in the brain [8]. Indeed, a wealth of evidence has shown that changes in the serotonin (5-HT) neurotransmitter may be an underlying mechanism of the disease [9, 10].

Serotonin plays a key role in a wide range of biological processes, in fact. Its actions are 5-HT mediated by a family of G-protein-coupled receptors referred to 5-HT<sub>1</sub>, 5-HT<sub>2</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, 5-HT<sub>5</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub>. The 5-HT receptors are highly expressed in the the brain, suggesting that they play a key role in the nervous system. These compounds are often utilized in the treatment of anxiety, epilepsy, obsessive-compulsive disorder, schizophrenia, sleep disorders, and

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\*Address correspondence to these authors at the Jilin Provincial Key Laboratory on Molecular and Chemical Genetics, The Second Hospital of Jilin University, Changchun 130041, P.R. China; Tel: 0086-0431-88796386; Fax: 0086-0431-88796386; E-mail: linyang1155@163.com and E-mail: xinli@jlu.edu.cn and School of Life Science Northeast Normal University, Changchun, Jilin 130024, P.R. China; E-mail: honglianghuo@hotmail.com

other diseases [11]. Pentylentetrazole (PTZ) is mainly used for acute infectious diseases, anaesthetic, and barbiturate poisoning induced respiratory depression, acute circulatory failure. Research shows that 5-HT<sub>3</sub> receptor excitement and antagonism can effectively change the PTZ induced clonic convulsion threshold in mice, implying that the 5-HT<sub>3</sub> receptor is involved in brain excitability and seizure discharge expression. On the contrary, selective 5-HT<sub>3</sub> receptor activity is enhanced under a high seizure threshold, demonstrating that the 5-HT<sub>3</sub> receptor may be useful in terms of treating seizures [10, 12].

In effort to better understand the relationship between epilepsy and the 5-HT<sub>3</sub> receptor, we carefully reviewed the extant research on epilepsy animal modeling, 5-HT receptors subunit distribution, and 5-HT<sub>3</sub> receptors as ligand gated ion channels; we also explored previous studies on the receptor activation, the relationship between the antagonist agent, and epilepsy pathogenesis establishment *via* gene knockout models. Finally, we compare the pathogenesis of epilepsy and depression to build an analogy that we hope will represent a new target for 5-HT<sub>3</sub> electrophysiological epilepsy treatment.

## 2. EPILEPSY MODEL

An appropriate epilepsy model is a crucial part of understanding the pathophysiology of epilepsy and the efficacy of anti-epileptic drugs. Epilepsy models can be *in vivo* or *in vitro*. The former includes the neuron model and the brain slice model, and are mainly used for drug screening and investigating anti-epileptic drug dose effect relationships. The latter include the acute epilepsy model, chronic epilepsy model, genetic epilepsy model, and resistant epilepsy model, and are utilized to represent different types of human epilepsy.

### 2.1. *In Vitro* Model

#### 2.1.1. Neuron Model

The neuron is the fundamental material exploited to establish any *in vitro* epilepsy. Researchers typically mouse cerebellar granule cells, cells from the cerebral cortex, and hippocampal neurons as the basis for the studies. The excitatory glutamate model is a relatively mature epilepsy model than can be used to induce a seizure like discharge that may be related to the excitatory NMDA receptor, which induces Ca<sup>2+</sup> influx and increase the concentration of Ca<sup>2+</sup> [13].

### 2.2. *In Vivo* Model

#### 2.2.1. Acute Epilepsy Model

The most significant existing acute epilepsy model is the maximum electric shock (MES) model, which is favored for ion channel drug research. Its use many results in certain drugs being selected for further research (*e.g.*, aminocaproic acid, tiagabine *etc.*), while others with anti-epilepsy effect are neglected [14], therefore people focus their attention on chronic epilepsy.

#### 2.2.2. Chronic Epilepsy

The chronic epilepsy model, kindling model, continuous epilepsy model and spontaneous epilepsy model have been

applied in studies on the pathophysiology of chronic epilepsy [15]. The kindling model uses repeated electrical and chemical stimulation of the thalamus, hippocampus, and other regions to show progressive epileptic activity in the EEG.

#### 2.2.3. Genetic Epilepsy Model

Researchers have used *in vivo* genetic models to investigate generalized seizures to find that the mechanism of the disease may be related to the degree of reticular nucleus activity, the characteristics of the membrane and state of the ion channel, the activity of proteins and enzymes, genetic and chromosomal mutations, and other factors [16].

#### 2.2.4. Resistant Epilepsy Model

The resistant epilepsy model has been used in studies on the treatment of intractable epilepsy and, as the name suggests, epilepsy resistance. These models include the lamotrigine-resistant kindled rat, the 6 Hz psychomotor seizure model of partial epilepsy model, and post-status epileptic models of temporal lobe epilepsy model [17].

Although, epilepsy model cannot imitate the whole process of the development of epilepsy in humans, the epilepsy model established provides a good basis for the pathogenesis of epilepsy research. At the same time, people can also through this model for screening of anti-epilepsy drugs. This also may provide a more in-depth understanding of the basis for the occurrence and development of epilepsy.

## 3. DISTRIBUTION AND FUNCTION OF 5-HT RECEPTOR SUBFAMILY

5-HT is a neurotransmitter which functions in the central nervous system (CNS) and peripheral nervous system (PNS) as well as in non-neural tissues (*e.g.*, those in the gastrointestinal, endocrine and cardiovascular systems). It also interacts with membrane receptor. It has many functions, including regulating emotion, appetite, sensations, cognition, pain, sleep, gastrointestinal motility, visceral sensitivity, and more [18]. There are seven types of 5HT receptors (5-HT<sub>1</sub> to 5-HT<sub>7</sub>) with various structure, conduction, and operation characteristics. The distribution and function of each of these receptors are shown in (Table 1).

5-HT<sub>1</sub> receptors are further divided into five categories: 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>1E</sub>, 5-HT<sub>1D</sub>, and 5-HT<sub>1F</sub>. The 5-HT<sub>1A</sub> receptor is mainly distributed in the CNS, and in human is located on the chromosome 5q11.2-q13 [19]. 5-HT<sub>1A</sub> knockout mice showed a reduced toxicity of the low-temperature response, which was thought to be mediated by the 5-HT<sub>1A</sub> receptor in the hypothalamus [20]. The human 5-HT<sub>1B</sub> receptor is located on chromosome 6q13; it is a G protein-coupled receptor which may promote the release of calcium [21, 22]. 5-HT<sub>1B</sub> knockout mice exhibit aggressive behavior, as well as increase in the regulation of impulsive behavior (which is not an increase in aggression itself) [23]. Any increase in 5-HT<sub>1B</sub> receptors is mainly regulated by short-term and long-term memory [24, 25]. 5-HT<sub>1D</sub> receptor has 374-377 amino acids without splice variants, and is associated with anorexia [26]. 5-HT<sub>1E</sub> receptor has been identified in the human frontal cortex on chromosome 6q14-q15, but their widespread distribution has not been confirmed [27,

**Table 1. Distribution and function of 5HT receptor subfamily.**

|                   | Distribution  | Function   |
|-------------------|---|--|
| 5-HT <sub>1</sub> | Central nervous system  | Depression, anxiety, insomnia  |
| 5-HT <sub>2</sub> | Central nervous system  | Nervous disorders  |
| 5-HT <sub>3</sub> | Sensory vagus nerve, intestine, sea horse CA1 area, amygdala, substantia nigra, brainstem | Epilepsy   |
| 5-HT <sub>4</sub> | Adrenal cortex  | Bowel movement   |
| 5-HT <sub>5</sub> | Cerebellar cortex hippocampus, only CA1 area of the hippocampus                           | Migraine   |
| 5-HT <sub>6</sub> | Brain regions such as striatum, limbic brain, and cerebral cortex                         | Understanding disorders, memory disorders, nervous division                          |
| 5-HT <sub>7</sub> | Pineal gland and hypothalamus   | Sleep, cognition, body temperature regulation, affective disorder, hormone secretion |

28]; the receptors are not expressed in rats or mice [29]. The 5-HT<sub>1F</sub> receptor gene is located on chromosome 3P11. It is speculated that the receptor may be a prime target for anti-migraine drugs [30].

5-HT<sub>2</sub> is divided into three categories: 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, and 5-HT<sub>2C</sub>. The 5-HT<sub>2A</sub> receptor gene is located on human chromosome 13q14-q21, and is encoded by 471 amino acids in the NPC mouse [31-34]. It is known to participate in the regulation of long-term memory and short-term memory [24, 25]. The expression of the 5-HT<sub>2B</sub> receptor has a significant impact on the cardiovascular system in mice [35]. The 5-HT<sub>2C</sub> receptor gene is located on human chromosome Xq24 with 458-5-HT<sub>2C</sub>; interestingly 460 amino acid receptor gene knockout mice are severely obese [36].

5-HT<sub>3</sub> receptors are divided into two classes: 5-HT<sub>3A</sub> and 5-HT<sub>3B</sub>, which are the only ligand gated ion channel receptors in the 5-HT receptor family [37]. So far, it has been confirmed that there are two genes encoding the 5-HT<sub>3</sub> receptor. The 5-HT<sub>3A</sub> receptor subunit contains 487 amino acids and, cysteine with high levels of Cys loop ligand gated ion channels (*e.g.*, nicotine, GABA, glycine receptor subunit II) 5-HT<sub>3B</sub> is a 441 amino acid encoding receptor [38], with a pentamer subunit that wraps around its composition and a central ion channel single subunit composed of a large extracellular N-terminal domain (ECD) [39], four trans membrane domain (M1-M4), and an extracellular C-terminal [40]; spiral portions of the amino acids in its large cell cycle assist ion permeation [41].

The 5-HT<sub>4</sub> receptor is located on chromosome 5q31-33. 5-HT<sub>4A</sub> and 5-HT<sub>4B</sub> are present in the bladder and kidney, while 5-HT<sub>4C</sub> and 5-HT<sub>4D</sub> are present in the brain and intestine [42]. 5-HT<sub>5</sub> includes 5-HT<sub>5A</sub> and 5-HT<sub>5B</sub>. The 5-HT<sub>5A</sub> receptor has 357 amino acids located on the human chromosome 7q36.1 [43]. It has been reported that 5-HT<sub>5A</sub> antagonists have antidepressant/anti-psychotic drug characteristics in animal models (Garcia-Ladona *et al.*, unpublished). The 5-HT<sub>5B</sub> receptor gene exists in the human chromosome 2q11-q13 and is not an encoded functional protein. 5-HT<sub>6</sub> is located in the chromosomal region of 1p35-p36, and is an antagonist on learning and memory function [44]. 5-HT<sub>7</sub> receptors are located on the human chromosome 10q21-q24

and have been shown to play a role in sleep, circadian rhythms, and mood [45].

#### 4. 5-HT INVOLVED IN THE PATHOGENESIS OF EPILEPSY

5-HT, as discussed above, is a neurotransmitter that functions in the CNS and PNS as well as several non-neuronal tissues that is involved in membrane receptor interaction [46]. The 5-HT system is involved in the pathogenesis of epilepsy and neuropathic pain. To be precise, 5-HT<sub>1A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, and 5-HT<sub>7</sub> receptors are involved in the occurrence and maintenance of epilepsy and in altered susceptibility to seizures [47-49]. 5-HT deficiency is the primary cause of seizures, and certain anti-epileptic drugs work by increasing the level of extracellular 5-HT receptors to produce anti-epileptic effect [50]. Lack of 5-HT<sub>2A</sub> receptors significantly increases the risk of seizure. The receptor may directly or indirectly control neuronal excitability throughout several network structures by interacting with the monoamine neurotransmitters GABA and glutamate [51].

The cerebral cortex nerve metabotropic and ionotropic 5-HT<sub>3</sub> receptor, 5-HT<sub>2</sub> (5-HT<sub>2rs</sub> and 5-HT<sub>3rs</sub>), is the main medium of excitatory 5-HT. The role of these receptors is related to intrinsic neuronal and synaptic excitability levels [52]. Studies have shown that activation of the 5-HT<sub>3</sub> receptor through SR57227 is related to PTZ-induced seizures and possibly related to hippocampal GABA activity [53]. Notable, among the 5-HT receptor family, only 5-HT<sub>3</sub> receptors are ligand gated ion channels that can directly or indirectly act by changing cell ion conductance or concentration leading to neuronal depolarization. It is not surprising, then, that any major shift in 5-HT receptors in the body is related to the induction of epilepsy [3].

##### 4.1. 5-HT<sub>3</sub> Receptor Ligand Gated Ion Channel

5-HT<sub>3</sub> receptors are ligand gated ion channel is located on the cell membrane which cause neuronal depolarization by changing the sodium ion, potassium, and calcium ion transmembrane [54, 55]. 5-HT<sub>3</sub> receptors are distributed in the entorhinal cortex, hippocampus CA1 area, amygdala, substantia nigra, and brainstem, and have strong expression.

Recent studies have shown that the entorhinal cortex, hippocampus CA1 area, amygdala, substantia nigra, and brainstem represent a common pathway in epilepsy pathogenesis. As opposed to the 5-HT<sub>2C</sub> receptor, as mentioned above, the 5-HT<sub>3</sub> receptor is a ligand gated ion channel receptor which mediates excitatory effect; accordingly, when 5-HT is combined with the 5-HT<sub>3</sub> receptor present in these regions into the target cells with high specificity and high affinity with the original combination, they can open non-selective cation channels, impact Na<sup>+</sup>, Ca<sup>2+</sup>, and K<sup>+</sup> influx and efflux, and produce an inward current. Thus, *via* postsynaptic depolarization, the voltage gated calcium channel is opened to produce excitatory postsynaptic potential and the epileptic impulses are transmitted and strengthened, resulting in epilepsy. This is consistent with the mechanism of glutamate induced epilepsy [56]. Further as a function of the cell, the calcium receptor is very important in cell signal transduction. At the same time, the concentration of chloride ions in the cell can change the GABA mediated depolarization leading to seizures [57]. In short, the 5-HT<sub>3</sub> receptor most certainly plays a crucial role in the control of epilepsy.

#### 4.2. 5-HT<sub>3</sub> Receptor Antagonists and Agonists

5-HT<sub>3</sub> receptors in the CNS, brainstem nuclei, end zone, nuclear solitary and spinal cord are relatively high, in the cortex, hippocampus, and amygdala [11b, 58]. *In vitro* experiments have shown that blocking the 5-HT<sub>3</sub> receptor in mice causes significantly delayed epileptic seizures induced *in vivo*, and may even stop them completely [52]. The anti-epileptic activity of selective 5-HT reuptake inhibitor has also been reported [59]. Ondansetron is a highly selective 5-HT<sub>3</sub> receptor antagonist, that has proven effective in treating several diseases such as anxiety, itching, refractory chronic diarrhea, irritable bowel syndrome, and epilepsy [60], and researchers have demonstrated its anticonvulsant potential in experimental seizure models as well [61, 62]. Other experiments have shown that adding the inhibitor causes the seizure rate of mice to increase [63]. According to shock experiments, the protective effect of Ondansetron may be due to the cation influx of change Na<sup>+</sup>, Ca<sup>2+</sup>, or K<sup>+</sup> leading to neuronal depolarization inhibition [61]. In a mouse model Ondansetron showed anticonvulsant effect against epileptic seizures in accordance with results obtained by Mohanty and Balakrishnan *et al.* [62].

PTZ, a c-aminobutyric acid (GABA) receptor antagonist, has been widely used in animal epilepsy models [64, 65]. Evidence suggests that the 5-HT<sub>3</sub> receptor can also be expressed through GABA in the hippocampus and cortex neurons [66, 67]. PTZ-induced seizure test have shown that in the present of PTZ [68], Ondansetron does not inhibit epileptic seizures. There also is neurochemical evidence that PTZ blocking factors are comprised mainly of the inhibition of GABA-mediated inhibitory effect. N-methyl-D-aspartate receptor and GABA participate in PTZ-induced seizure initiation and receptor propagation [63].

5-HT<sub>3</sub> is comprised of ligand gated ion channels and can regulate the activity of other neurotransmitters, such as norepinephrine, GABA, glycine, and dopamine and acetylcholine agents [54, 69-71]. The 5HT<sub>3</sub> receptor antagonist works as an inverse agonist benzodiazepine agent in GABA receptors

and as a GABA inhibiting agent [70, 72]. Ondansetron application has been shown to reverse the inhibition of GABA in rats in the anterior meningeal [73]. The exact mechanism of Ondansetron is unknown, but it may be related to enhance cholinergic brain functions as 5-HT<sub>3</sub> receptor heterogeneity modulates the activity of several neurotransmitters in the amygdala, cholinergic hippocampus, and glutamatergic system [74, 75]. SR57227 is a potent and selective agonist at the 5HT<sub>3</sub> receptor, with high selectivity over other serotonin receptor subtypes and good blood-brain barrier penetration [76]. Seizure latency was significantly increased in SR57227, in a manner significantly dependent on 5HT<sub>3</sub> receptor addition [10]. In an experimental group of mouse models with the receptor activator, the death rate of mice was also significantly decreased due to add SR57227 [10]. Altogether, the results described above have well established that the 5-HT<sub>3</sub> receptor is an important potential target for epilepsy treatment [10]. In many organisms, 5-HT and GABA is maintaining the balance of the nervous system. The levels of them are closely linked with neurophysiology, behavior, pathology, disease diagnosis and control [77]. Studies have shown that 5-HT can enhance GABA mediated inhibitory postsynaptic potential in rat hippocampal CA1 region [78]. Among the numerous types of 5-HT, the regulatory effect of 5-HT<sub>3</sub> receptor subtype on GABA was the most clear. 5-HT<sub>3</sub> receptors exist in layer I GABAergic neurons, a cortical level without pyramidal cells, indicates that 5-HT receptors can regulate the apical dendrites of input to pyramidal neurons in prefrontal cortex *via* 5-HT<sub>3</sub> receptors located in GABAergic interneurons [67]. In addition, activation of the 5-HT<sub>3</sub> receptors in the GABA neurons in the cortical 5-HT is able to inhibit the cholinergic function [78].

#### 4.3 Gene Knockout Model

“Gene knockout” refers to a genetic engineering technology where for a known sequence (but of unknown function) the gene is altered to block a portion of its function, then, the biological impact is analyzed to assess the comprehensive biological function of the target gene. In recent years, gene knockout has been applied in many fields. For example, in effort to determine the CNTNAP2 gene function, it was knocked out in a mouse model to find that it affects learning and memory function through its impact on the nervous system [79]. In another study, researchers attempted to establish Nox1y<sup>-</sup>, Nox2y<sup>-</sup>, or NOX4 genes as novel anti-angiogenesis therapy targets, using gene knockout technology. They found that the Nox4<sup>-</sup> gene in a mouse tumor model showed significant decrease in vessel formation density compared to the control, suggesting that NOX4 gene may be a new target in the treatment of tumor valuable anti-angiogenesis target [80].

Gene knockout mouse models have also been utilized to examine the relationship between 5-HT receptor subtypes and epilepsy. Mutant mice lacking the 5-HT<sub>2</sub> receptor subtype have been found to suffer death due to seizures [81], and 5-HT<sub>1A</sub> receptor gene knockout mice show reduction in seizure threshold and higher mortality [82]. 5-HT<sub>1A</sub> receptor single gene knockout mice have shown significant spatial memory impairment, suggesting that the 5-HT<sub>1A</sub> receptor subtype mediates spatial learning and memory [83].

Other studies on the 5-HT receptor gene, have investigated liver injury marker 5-HT transporter function by knocking out SERT (-/-) in mice and observing them in comparison to wild-type mice; 5-HT receptor knockout mice liver steatosis was significantly decreased, indicating that the gene was indeed missing, which is a key factor in fatty liver development [84].

In order to prove that the deficiency in brain 5-HT synthesis will affect animal behavior changes and neuroendocrine responses, then knock in mice tryptophan hydroxylase 2 gene and found that mice showed increased basal metabolism, reduce anxiety but strikingly increased conditioned fear responses, which indicates that the content of 5-HT in the brain does have an impact on the changes of animal behavior and neuroendocrine responses [85].

Engrailed 2 (EN2) as a possible autism susceptibility gene, EN2 knockout mice (EN2 -/-) 5-HT content decreased significantly in one and three months old mice, at the same time, the mice showed subtle cerebellar pathology change and tyrosine hydroxylase levels reduce [86]. Because knockout studies have confirmed the exact location of the 5-HT<sub>3</sub> receptor gene, it is highly likely that further knockout studies can be utilized to confirm the incidence rate of epilepsy in mouse models.

#### 4.4. Epilepsy and Depression

The coexistence of epilepsy and depression is an interesting (and potentially dangerous) psychiatric phenomenon. Epilepsy patients suffer a suicide rate four times higher than that of healthy people [87]. Treatment must not be limited to epilepsy itself, but must also be targeted toward neural, cognitive, and psychiatric complications which commonly coexist with epilepsy. Depression, for example, is very commonly present with epilepsy [88].

Norepinephrine and 5-HT deficiency have been shown to increase the incidence of certain forms of epilepsy and depression. Epidemiological investigation has confirmed the coexistence of these diseases, but also indicates that they are often difficult to read. Depression may actually be inextricably linked to epilepsy; interestingly, antidepressant drugs have anticonvulsant properties and anti-epileptic drugs can be used to treat affective disorders [89]. Research suggests that the 5-HT<sub>3</sub> receptor antagonist can increase single amine neurotransmitter release, which reflects a mechanism related to depression treatment [90]. These studies on 5-HT<sub>3</sub> and depression may provide a valuable reference for future research on novel epilepsy treatments.

#### 5. FUTURE RESEARCH DIRECTION

The treatment of epilepsy is a complex and lengthy process characterized by an unfortunate amount of uncertainty. They have indeed been many significant contributions to the literature in terms of innovative treatment techniques, but much work remains to be done. 5-HT, an important neurotransmitter in the CNS and PNS, is a receptor closely related to the onset and pathogenesis of epilepsy, a rather large quantity of research results support this relation. That said these results were established based on animal models, and we cannot be entirely sure whether there are identical or

similar mechanisms in the human body. Certainly though, the extant research discussed above represents an important future direction for further research on the 5-HT receptor as a novel target for epilepsy treatment.

#### CONSENT FOR PUBLICATION

Not applicable.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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