Association of the 5-HT_{2A} Receptor with Central Nervous System Disorders

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Abstract This article systematically reviews the structure, distribution, and signal transduction mechanisms of the 5-HT_{2A}R, with a particular focus on the association between its dysfunction and the pathogenesis of various central nervous system (CNS) disorders, including schizophrenia, depression, Alzheimer's disease, anxiety disorders, drug addiction, and sleep disorders. It further elaborates on the mechanisms of action and research progress of various drugs targeting the 5-HT_{2A}R (such as atypical antipsychotics, selective antagonists, and inverse agonists) in the treatment of these disorders. This review aims to provide insights for a deeper understanding of the pathophysiological functions of the 5-HT_{2A}R and for the development of more effective therapeutics for neuropsychiatric diseases.

Key words 5-HT_{2A}R, Schizophrenia, Depression, Alzheimer's disease, Anxiety disorders, Drug addiction, Sleep-Wake Cycle

1 Introduction

Serotonin receptors, also known as 5-hydroxytryptamine (5-HT) receptors, currently comprise 7 families and 14 subtypes. With the exception of the 5-HT_3 receptor, which is a ligand-gated ion channel, the others are all G protein-coupled receptors (GPCRs) that exert their effects by activating intracellular second messengers[1]. Among these, the 5-HT_2 receptor family includes the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors[2]. The 5-HT_{2A} receptor was initially described by Gaddum and Picarelli (1957) as the classical D receptor and was later defined as the 5-HT_2 receptor by Peroutka and Snyder in 1979[3]. This receptor is located on human chromosome 13 (13q14-q21), consists of 471 amino acids, possesses 5 potential glycosylation sites in the N-terminal extracellular region, and has 11 potential phosphorylation sites in the C-terminal intracellular region[4].

The 5-HT_{2A} receptor participates in regulating multiple intracellular signaling pathways, thereby influencing various higher-order neural functions such as cognition, emotion, and perception, and is involved in physiological processes like sleep and wakefulness. Recent research indicates that abnormalities in the structure and function of the 5-HT_{2A} receptor are closely associated with several central nervous system disorders, including schizophrenia, depression, Alzheimer's disease, anxiety disorders, and drug addiction. This article systematically reviews the signal transduction pathways associated with the 5-HT_{2A} receptor, explores its links to the aforementioned neurological disorders, and summarizes the mechanisms of action and research progress of current drugs targeting this receptor in the treatment of related diseases.

2 Overview of the 5-HT_{2A} receptor

2.1 Receptor molecular structure and distribution As a classic G protein-coupled receptor, the 5-HT_{2A} receptor is composed of seven transmembrane α-helical domains. Ligand binding induces a conformational change in the receptor, leading to the dissociation and activation of specific heterotrimeric G proteins into α and β subunits. These dissociated subunits then elicit diverse cellular effects through different downstream effectors[5].

The 5-HT_{2A} receptor is widely distributed throughout the central nervous system. Its expression is highest in the frontal cortex, hippocampus, hypothalamus, and basal ganglia, with significant expression also observed in the ventral striatum, amygdala, substantia nigra, and visual cortex[6-7]. This receptor is involved in numerous central physiological functions, including memory, cognition, emotion, and sleep[8], and is also implicated in central nervous system disorders such as schizophrenia, depression, Alzheimer's disease, anxiety disorders, drug addiction, and insomnia[9-10].

2.2 Signal transduction pathways Following activation, the 5-HT_{2A} receptor primarily exerts its effects via the classical Gαq/11-PLC-IP3 pathway. Upon coupling with Gαq/11, the 5-HT_{2A} receptor activates phosphoinositide-specific phospholipase C-beta (PLCβ). The activated PLCβ then catalyzes the hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP2) in the cell membrane into inositol-1,4,5-triphosphate (IP3) and diacylglycerol (DAG). IP3 stimulates the release of intracellular calcium ions from the endoplasmic reticulum[11] and activates calcium/calmodulin-dependent protein kinase II (CaMKII). The DAG pathway activates protein kinase C (PKC), which in turn activates extracellular signal-regulated kinase (ERK), among others, and the downstream transcription factor cAMP-response element binding protein (CREB), thereby regulating gene expression[12-13].

Research by Kurrasch-Orbaugh *et al.* using NIH3T3-5HT_{2A}R cells demonstrated that the 5-HT_{2A} receptor can also induce the production of free arachidonic acid (AA) through a complex signaling cascade, and this process is independent of the PLC activation mediated by Gαq coupling to the 5-HT_{2A} receptor[14]. Further studies have established that the 5-HT_{2A} receptor can activate pertussis toxin-sensitive Gαi/o proteins. Upon activation, Gαi/o dis-

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sociates from Gβγ, and the Gβγ complex can initiate the activation of the Ras-Raf-MEK1/2-ERK1/2 signaling cascade. Ultimately, ERK mediates the activation of phospholipase A2 (PLA2)[15].

Gαi is an inhibitory G protein subtype, while Gαs is a stimulatory G protein. Together, they regulate the activity of adenylate cyclase (AC), influencing the formation of intracellular cyclic adenosine monophosphate (cAMP). cAMP acts as a second messenger that activates protein kinase A (PKA), which in turn participates in regulating numerous downstream target proteins[16]. In addition to coupling with G proteins, the 5-HT_{2A} receptor can also couple with the intracellular scaffolding protein β-arrestin2. This coupling facilitates the activation of Akt phosphorylation in frontal cortex and primary cortical neurons through the β-arrestin2/PI3K/Src/Akt cascade[17].

2.3 Receptor functional selectivity The 5-HT_{2A} receptor can be activated by different ligands, which then selectively activate specific signaling pathways. This characteristic is termed "ligand-biased signaling" or "functional selectivity". This means that when different ligands bind to the 5-HT_{2A} receptor, they can stabilize distinct conformational states of the receptor. This preferential stabilization leads to the preferential activation of specific downstream pathways while relatively suppressing others, ultimately resulting in divergent functional effects[18]. The functional selectivity of the 5-HT_{2A} receptor elegantly explains why some 5-HT_{2A} receptor agonists produce hallucinogenic effects, while others, such as lisuride, are non-hallucinogenic.

3 Association of the 5-HT_{2A} receptor with central nervous system disorders

3.1 Schizophrenia Schizophrenia is a severe chronic mental disorder characterized primarily by disorganized thinking, abnormal behavior, and cognitive dysfunction. The classical dopamine hypothesis posits that the positive symptoms of schizophrenia, such as hallucinations and delusions, are primarily associated with hyperfunction of dopaminergic neurotransmission in the mesolimbic dopamine system. Conversely, the negative symptoms, including affective flattening, social withdrawal, and cognitive impairments, are mainly caused by hypofunction of dopamine in the mesocortical pathway[19-21]. The first-generation antipsychotic drugs that emerged from this hypothesis, such as chlorpromazine and haloperidol, primarily alleviate positive symptoms by blocking D2 receptors. However, they lack efficacy against negative symptoms and may even exacerbate them, and are associated with severe extrapyramidal side effects (EPS)[22].

The discovery of clozapine presented a challenge to the dopamine hypothesis. Clozapine is highly effective in treatment-resistant schizophrenia patients, yet it exhibits relatively low affinity for the dopamine D2 receptor while possessing very high affinity for the 5-HT_{2A} receptor[23]. Concurrently, research into the central effects of the hallucinogen lysergic acid diethylamide (*LSD*) and its resemblance to schizophrenia symptoms further implicated the 5-HT_{2A} receptor in the disorder[24-25]. Consequently, second-generation atypical antipsychotic drugs, such as clozapine, aripiprazole, iloperidone, and olanzapine, primarily combine effective blockade of the 5-HT_{2A} receptor with weak antagonism of the dopamine D2 receptor. According to statistics by Kusumi I *et al.*, first-generation typical antipsychotics preferentially occupy D2 receptors, having minimal or no effect on the 5-HT_{2A} receptor. In contrast, second-generation atypical antipsychotics exhibit significantly higher binding affinity for the 5-HT_{2A} receptor compared to the D2 receptor[26].

Antagonism of the 5-HT_{2A} receptor can enhance dopaminergic transmission in the nigrostriatal pathway, thereby reducing the risk of extrapyramidal side effects. Furthermore, it can ameliorate the negative symptoms and cognitive impairments of schizophrenia by increasing the release of dopamine and acetylcholine in the prefrontal cortex[27].

Acute administration of NMDAR antagonists such as phencyclidine (PCP), MK-801, or ketamine disrupts corticothalamic glutamatergic neurotransmission, leading to aberrant hyperactivity. This model is widely regarded as representative of schizophrenia. The selective 5-HT_{2A} receptor antagonist M100907 significantly ameliorated motor deficits in an MK-801-induced schizophrenia model in mice[28]. Moreover, in PCP-induced models of visual and memory impairments, the 5-HT_{2A} receptor inverse agonist pimavanserin and the antagonist M100907, when co-administered with atypical antipsychotics, reversed PCP-induced deficits in novel object recognition, thereby improving cognitive dysfunction associated with schizophrenia[29].

Literature indicates that the phosphorylation level of glycogen synthase kinase-3β (GSK-3β) at Ser9 is reduced in the brains of schizophrenia patients. Part of the mechanism underlying the efficacy of atypical antipsychotic drugs may involve their antagonism of 5-HT_2 receptors, which increases GSK-3β (Ser9) phosphorylation, thereby inhibiting GSK-3β activity. GSK-3β is a key regulator of hippocampal neural progenitor cell proliferation. Inhibition of its activity promotes β-catenin nuclear translocation. This subsequently upregulates cyclin D1 transcription, accelerates the transition of the cell cycle from the G_1 to S phase, and enhances hippocampal neural progenitor cell proliferation[26, 30]. Additionally, these drugs may exert neuroprotective effects by increasing levels of brain-derived neurotrophic factor (BDNF). BDNF can further promote the phosphorylation of GSK-3β via the TrkB pathway[26].

3.2 Depression Depression is a chronic mental disorder affecting over 350 million people worldwide. It manifests as persistent sadness, diminished interest, impaired concentration, and physical symptoms such as chronic pain, fatigue, and sleep disturbances. Current pharmacological treatments for depression primarily include: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants. As these agents largely exert their effects

indirectly, they share two common limitations: a delayed onset of action and often suboptimal efficacy. Achieving significant clinical improvement typically requires prolonged administration, with treatment sometimes needing to be maintained for years to prevent relapse[31].

As early as 1980, Peroutka SJ, Snyder SH, and colleagues, utilizing the high-affinity radiolabeled ligand spiperone for the 5-HT_{2A} receptor, reported that chronic administration of tricyclic antidepressants like desipramine and amitriptyline significantly downregulated 5-HT_{2A} receptors in the rat frontal cortex[32]. Subsequently, Klimek V *et al.* found that repeated administration of the selective serotonin reuptake inhibitor citalopram similarly downregulated 5-HT_{2A} receptors[33]. This suggests that downregulation of the 5-HT_{2A} receptor may represent a common mechanism underlying the therapeutic action of antidepressant drugs[10]. Furthermore, post-mortem brain studies in suicide victims, utilizing[(125)I] LSD binding, protein expression, and mRNA analysis, confirmed elevated levels of 5-HT_{2A} receptors, protein, and mRNA in the prefrontal cortex and hippocampus—regions critically involved in mood regulation, stress response, and cognition[34].

In recent years, a growing body of research has revealed that certain atypical antipsychotics can enhance the clinical response to SSRIs in patients with treatment-resistant depression. Significantly, these antipsychotics all possess the ability to block 5-HT_{2A} receptor-mediated responses in the brain at clinically relevant doses[35], suggesting that combining a 5-HT_{2A} receptor antagonist with an SSRI may augment their antidepressant efficacy in individuals with major depressive disorder. For instance, Ostroff RB *et al.* reported rapid symptomatic relief within one week in eight patients with severe, non-psychotic major depression who had previously shown no response to SSRI monotherapy, following adjunctive treatment with the 5-HT_{2A} receptor antagonist risperidone. This indicates that risperidone can augment the clinical effectiveness of SSRIs in SSRI non-responders[36]. Similarly, Shelton RC *et al.* reported minimal improvement in 28 patients with non-psychotic, treatment-resistant depression when treated with the selective serotonin reuptake inhibitor fluoxetine or the atypical antipsychotic olanzapine alone. However, combined fluoxetine and olanzapine administration resulted in significantly improved therapeutic outcomes without notable adverse effects[37].

Collectively, these findings indicate that a 5-HT_{2A} receptor antagonist alone does not produce a robust antidepressant effect. Its efficacy in depression treatment appears to require combination with antidepressants acting on other targets to either initiate a response or enhance therapeutic potency. Consequently, the development of multitarget antidepressants that include 5-HT_{2A} receptor antagonism among their mechanisms holds promise as an effective therapeutic strategy for depression.

3.3 Alzheimer's disease Alzheimer's disease (AD) is a prevalent neurodegenerative disorder characterized by progressive cognitive decline, memory loss, and impairment in activities of daily living. It represents the most common form of dementia, accounting for approximately 60% – 80% of dementia cases[38]. The 5-HT_{2A} receptor is abundantly distributed in brain regions critical for cognition and memory, particularly the prefrontal cortex and hippocampus[6]. Furthermore, polymorphisms in the human HTR2A gene have been linked to alterations in memory processes. Specifically, a polymorphism resulting in the substitution of histidine (His) by tyrosine (Tyr) at residue 452 of the receptor subunit is associated with significant impairments in memory and recall function[39], implicating the 5-HT_{2A} receptor in the pathology of Alzheimer's disease.

Amyloid precursor protein (APP) undergoes proteolytic cleavage at the cell membrane[40]. One cleavage pathway, mediated by α-secretase, generates soluble APP α (sAPPα), while an alternative pathway, mediated by β-site APP cleaving enzyme (BACE), produces β-amyloid peptide (Aβ) monomers[41]. Under pathological conditions, increased BACE activity predominates, leading to excessive Aβ production. Aberrant aggregation of Aβ into plaques triggers neuronal toxicity, activating microglia and astrocytes. This activation prompts the release of abundant pro-inflammatory cytokines and reactive oxygen species, inducing oxidative stress and neuroinflammation. These processes further contribute to the abnormal hyperphosphorylation of microtubule-associated protein tau (Tau), culminating in the formation of neurofibrillary tangles (NFTs). The primary neuropathological hallmarks of Alzheimer's disease are thus β-amyloid plaques and neurofibrillary tangles resulting from aberrant Tau phosphorylation[42].

Yuede *et al.* administered the 5-HT_{2A} receptor inverse agonist pimavanserin and the 5-HT_{2A} receptor antagonist M100907 to APP/PS1 double-transgenic AD model mice. Using in vivo microdialysis, they monitored Aβ levels in the brain interstitial fluid in real-time. Their results demonstrated that both compounds reduced Aβ levels in the interstitial fluid by nearly 50% within hours. Furthermore, chronic administration of pimavanserin to APP/PS1 mice reduced amyloid plaque burden in the AD mouse brains and improved cognition-related behavioral performance. However, the study found that pimavanserin did not alter α-secretase activity, suggesting that the reduction in Aβ levels likely involves enhanced clearance mechanisms, the specifics of which warrant further investigation[43].

Lu J *et al.* discovered that desloratadine, a first-line clinical antihistamine acting as a selective 5-HT_{2A} receptor antagonist, effectively ameliorated pathological alterations in APP/PS1 mice. Employing APP/PS1 mice with 5-HT_{2A} receptor knockdown to validate the underlying mechanism, they demonstrated that desloratadine, via selective 5-HT_{2A} receptor antagonism, activates the 5-HT_{2A}R/cAMP/PKA/CREB/Sirt1 signaling pathway. This activation stimulates autophagy and promotes nuclear translocation of the glucocorticoid receptor. Consequently, this leads to the upregulation of phagocytic receptor transcripts TLR2 and TLR4, enhancing microglial phagocytosis and degradation of Aβ, reducing amyloid plaque deposition, and polarizing microglia toward an anti-inflammatory phenotype to ameliorate innate immune

responses[44].

As indicated by prior research, antagonism of the 5-HT_{2A} receptor activates phosphorylation of GSK-3β at Ser9, thereby inhibiting its kinase activity and preventing it from catalyzing downstream substrates. Following inhibition of its activity, GSK-3β suppression reduces BACE gene expression by downregulating the NF-κB signaling pathway: conversely, activated GSK-3β promotes nuclear translocation of NF-κB/p65 and its binding to the BACE promoter, thereby upregulating BACE protein levels and Aβ production[45]. Thus, phosphorylation (inactivation) of GSK-3β serves to diminish BACE activity and reduce Aβ generation. Furthermore, as GSK-3β is a major kinase responsible for Tau phosphorylation, its inhibition also reduces Tau hyperphosphorylation, thereby preventing the formation of neurofibrillary tangles[46].

3.4 Anxiety disorders Anxiety disorders are psychiatric conditions characterized by excessive and persistent feelings of anxiety as their core feature, typically accompanied by physical symptoms such as palpitations and tremors, as well as cognitive symptoms like difficulty concentrating. Research indicates that serotonin (5-HT) within the central nervous system plays a role in modulating anxiety-like behaviors in both humans and rodents. Furthermore, 5-HT_{2A} receptors are densely distributed in brain regions implicated in emotion and anxiety regulation, including the cerebral cortex, amygdala, and ventral striatum[47-48].

Weisstaub NV *et al.*, utilizing mice with genetically ablated 5-HT_{2A} receptors and employing behavioral tests such as the open field test, light/dark box test, elevated plus maze, and novelty-suppressed feeding test, observed reduced anxiety-like behaviors in the knockout mice. These mice spent more time in the center of the open field and explored the illuminated compartment longer in the light/dark box. This demonstrates that 5-HT_{2A} receptor signaling participates in the regulation of anxiety-like behaviors in mice[48]. Sarkar A *et al.* further discovered that postnatal treatment with the serotonin reuptake inhibitor fluoxetine induces anxiety behaviors in adult rodents. Crucially, administration of a selective 5-HT_{2A} receptor antagonist was able to block these fluoxetine-induced anxiety behaviors and normalize the specific gene expression changes observed in the prefrontal cortex[49].

3.5 Psychotic symptoms (hallucinations) Psychotic symptoms, such as hallucinations and delusions, frequently accompany the progression of various neuropsychiatric disorders. For instance, up to 50% of patients with Parkinson's disease (PD) develop psychotic symptoms, termed Parkinson's disease psychosis (PDP), in the later stages of the illness[50]. Studies have revealed increased binding of 5-HT_{2A} receptors in the cerebral cortex of PD patients. Moreover, visual hallucinations have been specifically linked to elevated 5-HT_{2A} receptor numbers within brain regions responsible for visual processing. Pimavanserin, developed by Acadia Pharmaceuticals Inc. in the US, is a selective 5-HT_{2A} receptor inverse agonist. It exhibits high selectivity for the 5-HT_{2A} receptor and lacks significant dopaminergic, adrenergic, or histaminergic activity[51]. In 2016, the US FDA formally approved the 5-HT_{2A} receptor inverse agonist pimavanserin as the first and only medication specifically indicated for the treatment of PDP.

Furthermore, post-mortem and genetic studies indicate that psychotic symptoms, including hallucinations and delusions, associated not only with PDP but also with conditions like AD and dementia with Lewy bodies, are linked to alterations in the serotonergic (5-HT) system. In 2018, Ballard C *et al.* treated 181 patients with Alzheimer's disease psychosis with either pimavanserin or a placebo. By the sixth week of treatment, they observed symptom improvement in patients receiving pimavanserin[52]. In another trial focused on dementia-related psychosis, the therapeutic effect of pimavanserin was evaluated in patients with psychosis associated with Alzheimer's disease, Parkinson's disease dementia, dementia with Lewy bodies, frontotemporal dementia, and vascular dementia. Among the 351 patients enrolled, 217 exhibited a sustained response to pimavanserin. Further analysis demonstrated that patients with dementia-related psychosis who continued treatment had a lower risk of relapse compared to those who discontinued the medication[53].

3.6 Drug addiction Post-mortem brain examinations of opioid addicts revealed functional alterations in the Gαq/11 signaling pathway mediated by the coupling of 5-HT_{2A} receptors with M1 muscarinic acetylcholine receptors in the prefrontal cortex. This alteration may partially underlie the addictive behaviors associated with opioids[54]. Li B *et al.* administered heroin to C57BL/6J mice to induce heroin dependence. They observed that heroin upregulated 5-HT_{2A} receptors and suppressed ERK phosphorylation in the prefrontal cortex. Subsequently, naloxone was administered to precipitate withdrawal symptoms, followed by the 5-HT_{2A} receptor antagonist M100907. Behavioral assessment demonstrated that inhibiting 5-HT_{2A} receptors attenuated naloxone-induced withdrawal symptoms[55].

The underlying neurobiology of dependence and relapse behaviors following prolonged abstinence in drug addiction involves the modulation of serotonergic (5-HT) neurotransmission. Cunningham KA *et al.* investigated the effects of combining the selective 5-HT_{2A} receptor antagonist M100907 with the 5-HT_{2C} receptor agonist WAY163909 on cocaine addiction behaviors. Their results showed that the synergistic action of these two drugs significantly suppressed cocaine-induced hyperactivity, impulsivity, and cocaine-seeking behavior following withdrawal[56]. These findings also highlight the therapeutic potential of bifunctional ligands targeting both 5-HT_{2A} and 5-HT_{2C} receptors as anti-addiction medications, laying the groundwork for developing novel ligands with enhanced efficacy and selectivity.

3.7 Sleep-Wake Sleep disorders, such as acute and chronic insomnia, have become prevalent clinical issues, characterized by difficulties in initiating or maintaining sleep, as well as poor sleep quality. The serotonergic (5-HT) system within the dorsal raphe nucleus plays a key role in regulating sleep-wake behaviors in the central nervous system. 5-HT_{2A} receptors have been demonstrated to modulate slow-wave sleep (SWS), with numerous studies re-

porting that the 5-HT_2 receptor antagonist ritanserin significantly enhances SWS[57-58]. In the search for effective treatments for sleep disorders, the 5-HT_{2A} receptor subtype has emerged as significantly involved in managing both primary and secondary sleep disturbances[59]. Griebel G *et al.* demonstrated that 5-HT_{2A} receptor antagonists such as eplivanserin and volinanserin can increase the duration of non-rapid eye movement (NREM) sleep while simultaneously reducing wakefulness, and that these antagonists can act synergistically with the hypnotic drug zolpidem[60]. However, the precise mechanism by which 5-HT_{2A} receptor antagonism improves slow-wave sleep remains incompletely understood. Serotonergic neurons in the dorsal raphe nucleus of both rodents and humans receive inhibitory input from GABAergic cells and interneurons located in multiple regions of the basal forebrain and brainstem. It is proposed that 5-HT_{2A} receptor antagonists may promote slow-wave sleep by reducing this inhibitory input to sleep-active neurons in the ventrolateral preoptic area (VLPO)[61].

4 Conclusions

In summary, the 5-HT_{2A} receptor, a critical target within the central nervous system, has been firmly established as a key regulator of diverse neuronal activities, as well as processes encompassing cognition, emotion, and perception. Coupled to multiple signaling pathways in the CNS, functional and structural aberrations of this receptor are closely linked to the pathological progression of various disorders, including schizophrenia, depression, and AD. These findings provide crucial insights for the diagnosis and treatment of these conditions. Although significant progress has been made in current research on the 5-HT_{2A} receptor, numerous unresolved questions persist, such as the nature of its cooperative interactions with other neurotransmitters and the differential selectivity profiles of its agonists and antagonists. The complex roles of the 5-HT_{2A} receptor within the CNS demand further exploration to advance the development of more effective and safer therapeutic agents for neuropsychiatric disorders.

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