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Research progress of G protein-coupled receptor drugs in nervous system diseases

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ABSTRACT
This review explores the research progress of G protein-coupled receptors (GPCRs) in neurological diseases, highlights the central role of GPCRs in the regulation of cognitive function and mood, and discusses their potential therapeutic potential in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. This review also covers the importance of adhering GPCRs (aGPCRs) in neurodevelopment and discusses the application of structural biology, gene editing, and artificial intelligence in GPCR drug development. Future studies will focus on revealing the detailed mechanism of action of GPCRs to develop more effective therapies.

KEYWORDS
G protein-coupled receptors (GPCRs); Nervous system diseases; Drug development; Adherent GPCRs (aGPCRs)

1 Introduction

Nervous system diseases are a complex group of pathological conditions affecting millions of patients worldwide, ranging from cognitive impairment to motor dysfunction. Examples include multiple sclerosis, Parkinson's disease, and Alzheimer's disease. As society ages, patients with degenerative diseases are becoming more prevalent, and there is a growing need for efficient treatment. The neurological system depends heavily on G protein-coupled receptors (GPCRs), important cell signaling mediators. In particular, adhesive G protein-coupled receptors (aGPCRs) have become the focus of research due to their roles in neurodevelopment and disease progression. Although the potential role of GPCRs in neurological diseases has been widely recognized, the detailed mechanisms and therapeutic potential of GPCRS remain to be explored. This review will focus on the research progress of GPCRs in neurological diseases, assess their potential as drug targets, and discuss current drug development strategies. By analyzing the role of GPCRs in nervous system function and diseases, this review aims to provide a new perspective for understanding and treating neurological diseases, and at the same time point out the direction for future research and drug development.

2 An overview of GPCRs

G protein-coupled receptors (GPCRs) are a substantial family of cell surface receptors integral to cellular function.[1] in modulating cellular responses to diverse inputs. By interacting with specific G proteins, these receptors activate a variety of intracellular signaling pathways, thereby affecting cell behavior and function[2]. According to Robert Fredriksson and others[3] in A 2003 study, GPCRs can be divided into five main family, class A, also called rhodopsin receptor, is the largest number of family, including visual and olfactory receptors; Class B, or secretin-like receptors, bind primarily to peptide hormones; Class C, metabolic receptors, represented by glutamate receptors, which play a key role in the nervous system; Class D, fungal mating receptors, which mainly play a role in fungi; Frizzled/Smoothened class, involved in the regulation of Wnt signaling pathway. In addition, adhesive GPCRs (aGPCRs) as a GPCR superfamily of a unique branch, has a unique structure characteristics and biological function of them in disease treatment and shows great potential in drug development. These receptors' diversity and signaling properties make them valuable targets for drug discovery, particularly in the creation of psychoactive drugs, where functional selectivity[4] offers a novel method of engaging particular pathways in the pleiotropic signaling repertoire of G protein-coupled receptors at specific times. These drugs, which selectively activate signaling pathways linked to positive clinical outcomes, are the first instances of signaling-biased medications for the μ-opioid receptor and the angiotensin II receptor to reach clinical trials. The most recent example of a functionally selective ligand is a dual steric/bisteric hybrid molecule (a ligand that combines at least two pharmacophores). They can effectively degrade receptor flexibility and reasonably create signal transduction bias due to their binding structure.

Selective function concept further extend our understanding of GPCRs, shows how different ligands by unrael the activation of specific signaling pathways to produce different biological effects. Such knowledge is essential for the design of drugs with specific therapeutic effects. Although significant progress has been made in the study of GPCRs, a deeper understanding of their roles in different physiological and pathological processes remains an active area of

biomedical research.

3 GPCRs and nervous system diseases

G protein-coupled receptors (GPCRs) are essential in the neurological system. They participate in the control of cognitive function, emotion, behavior, and neurotransmitter secretion. Due to the central role[5] of GPCRs in neural signal transduction, they have become a focal point in the management of neurological disorders.

Studies have shown that the dysfunction of GPCRs is associated with a variety of nervous system diseases, including Alzheimer's disease, Parkinson's disease, depression, anxiety, schizophrenia, and so on. For example, the 5-HT6 receptor, a member of the GPCR family, has become the focus of research due to its role in learning and memory formation. Nirogi et al.[6] noted in their 2023 review that 5-HT6 receptor antagonists have shown the ability to improve cognitive function in preclinical models, and despite inconsistent results in phase III clinical trials in Alzheimer's disease, they may play a role in managing neuropsychiatric symptoms of dementia.

The potential of peptide ligand[7] GPCRs as neurotherapeutic agents was explored in the 2020 review by Eiden et al. They noted that peptide ligand GPCRs have unique roles in regulating behavioral and physiological responses and may offer innovative approaches for addressing obesity, addiction, anxiety disorders, and neurodegenerative diseases, among others.

The 2019 study by O'Brien et al.[8] focused on RGS proteins, which act as regulators of GPCR signaling. They discussed the role of RGS proteins in disease states, particularly in cancer and neurological diseases. By regulating the activity of GPCRs, RGS proteins may influence neurotransmitter release and signaling, thereby playing a role in the treatment of neurological diseases.

Indeed, with regard to the pharmaceutical potential of GPCRs in neurological diseases, an in-depth discussion was conducted in 1995 by Bockaert and Pin, who explored GPCRs (G protein-coupled receptors) as potential targets for psychoactive drugs. They highlighted the great potential of these receptors in the treatment of nervous system diseases, demonstrating the critical role of GPCRs in regulating neurotransmitter substances and signaling pathways. Through their study, we can see the importance of GPCRs in the treatment of such neurological diseases as depression, anxiety, schizophrenia, and many others. Their work lays the foundation for future research, reveals the broad prospects of GPCRs as drug targets, and provides new ideas for the development of new therapeutic approaches.

In summary, despite the great potential of GPCRs in the treatment of neurological diseases, there are still challenges in translating these research findings into clinical applications. For example, drug selectivity, side effects, drug resistance, as well as the brain permeability of drugs need to be addressed. In addition, the complex role of GPCRs in different diseases also needs to be further studied.

3.1 The potential of GPCRs as drug targets

The potential of GPCRs as drug targets in the treatment of nervous system diseases has been widely recognized. A variety of drugs targeting GPCRs have been successfully used in clinical practice, providing effective means for the treatment of a variety of nervous system diseases.

According to the Parkinson's Disease Research Group, pramipexole was more effective than levodopa in reducing [123I] β-CIT uptake in the striatum of PD patients, which may indicate a potential neuroprotective effect of pramipexole in slowing disease progression. This is further supported by the experimental results of Izu et al., who[9] found that pramipexole was able to significantly reduce the death of dopaminergic neurons induced by glutamate, and this protective effect was most evident at a concentration of 1 mM. Pramipexole safeguards dopaminergic neurons against glutamate neurotoxicity by lowering intracellular dopamine levels. This protective effect is not dependent on the activation of dopamine D2-like receptors but is achieved through a direct reduction of dopamine content. Both the S(−) and R(+) enantiomers of pramipexole showed similar protective effects, suggesting that this effect was independent of its nature as a dopamine D2-like receptor agonist.

Pramipexole exerted its neuroprotective effect on the dopamine system by reducing the intracellular dopamine content, which was significant and reversible at the concentration of 10 μM. In addition, pramipexole also showed a scavenging effect on the white amino acid pigment O-semiquinone free radical, which may be another mechanism of its neuroprotective effect.

On the other hand, in exploring individual differences in the treatment of depression, a study applying the gradient boosting method (GBM) found that age was the strongest predictor of response to placebo treatment, which may be used to explain the higher rate of response to placebo in younger patients. In addition, among patients with current depressive episodes of approximately 12 weeks' duration, duloxetine showed a higher probability of response than SSris, suggesting that duloxetine may be an effective option for treating depressive episodes of moderate duration. At the same

time, the HAMD17 core symptoms and anxiety scale scores of SSRI treatment effect is greater than placebo, this might mean for patients with symptoms of heavier, SSRI may be a more appropriate treatment options. It is worth noting that BMI have less effect on the treatment to relieve, suggests that when predicting treatment response, BMI may not be a key factor. The higher probability of response with duloxetine than with SSRI or placebo in patients without a previous depressive episode suggests that duloxetine may be the treatment of choice for patients with a first episode of depression. Finally, regional differences also had an effect on treatment response, with higher probabilities of response among non-U.S. patients than among U.S. patients and an advantage of duloxetine over SSris for U.S. patients. These findings highlight the importance of accounting for individual differences in the treatment of depression and provide clinicians with a scientific basis to consider these factors when selecting treatment options.

With regard to the treatment of depressive disorders, Fluoxetine has shown similar overall therapeutic effects as tricyclic antidepressants (such as imipramine, amitriptyline, and doxepin) in clinical trials. Fluoxet[10]ine has shown significant efficacy compared with placebo in the treatment of patients with unipolar depression. In five to six weeks of control study, the curative effect of fluoxetine and tricyclic antidepressants, and less anticholinergic side effects. In patients treated with fluoxetine for more than 6 months, symptom improvement was maintained and recurrence rates were low and similar to imipramine. Common side effects of fluoxetine include nausea, nervousness, and insomnia, but they are usually not serious. It causes significantly fewer anticholinergic side effects (e.g., dry mouth, constipation) than tricyclic antidepressants. It has a slight heart rate lowering effect. The main mechanism of action and efficacy of fluoxetine in treating depression is largely attributed to its inhibitory effect on serotonin transporter.

Fluoxetine is a valuable alternative in the treatment of depression, especially in patients who cannot tolerate the side effects of tricyclic antidepressants.

3.2 The special case of adhesion GPCRs (aGPCRs)

Adhesive G protein-coupled receptors (aGPCRs) are an important class of cell surface receptors that play a role in a variety of physiological processes, including organ formation, neural development, and myelination, which are essential for maintaining the integrity and function of the nervous system.

Given their diverse roles, it is not surprising that aGPCRs are potential therapeutic targets for neurological diseases. For example, mutations in several aGPCRs have been associated with human diseases, underscoring their importance in health and disease. Recent advances in the understanding of the activation mechanisms of aGPCRs, such as the role of self-cleaving and peptopeptide agonists, have provided a basis for exploring their complex signaling pathways.

Specifically, the review by Vizurraga et[11] al. (2020) provides a detailed layout of current theories regarding the mode of activation of agPcrs, which is essential for developing pharmaceutical interventions. In addition, the study by Folts et al. (2019) [12] highlights the untapped potential of agPtrs as drug targets for neurological diseases, discussing their recent insights in biological function and disease relevance. Together, these studies highlight the importance of aGPCR in the context of neurological diseases and the need for further research to fulfill its therapeutic potential.

However, Ganesh[13] proposed that GPR56 might be a significant therapeutic target for neuropsychological conditions. GPR56, also called GPR56/ADGRG1, is a member of the adherents G protein-coupled receptor (aGPCR) ADGRG subgroup. The biggest family of membrane protein receptors in the human genome, the GPCR superfamily, has Agpcrs as its second-largest subfamily. According to recent research, GPR56 is essential for healthy brain development and has a significant impact on cortical growth. Indeed, some neurological and behavioral conditions, such as epilepsy, depression, and bilateral frontoparietal polymicrogyria (BFPP), have been linked to aberrant GPR56 expression. In an animal model of depression, up-regulation of GPR56 was observed to decrease depressive-like behaviors, indicating that GPR56 is crucial for antidepressant responses. Research has focused on GPR56's function because it correlated with antidepressant reactions. GPR56's role in neurological and psychiatric diseases like BFPP, epilepsy, depression, and autism is reviewed. Examining GPR56 signaling and activity under these conditions suggests that it may be a good target for antidepressants. However, it is important to note that the detailed molecular mechanisms remain largely unexplored.

3.3 Innovative strategies for drug development of GPCRs

G protein-coupled receptors (GPCRs) serve as significant drug targets in drug research and development, which remains a focal point of ongoing investigation. With the progress of science and technology, especially the breakthroughs in structural biology, gene editing and artificial intelligence, innovative strategies for drug development of GPCRs continue to emerge.

3.3.1 Precision drug design guided by structural biology

Structural biology plays a crucial role in the field of modern drug research and development. By using cutting-edge

techniques such as X-ray crystallography and cryoelectron microscopy, scientists have been able to precisely dissect the three-dimensional structures of G protein-coupled receptors (GPCRs). These structural information provide a solid foundation for drug design, making the drug development process more precise and efficient.

As for the serotonin receptor, it is involved in learning, mood, and sleep and is the target of drugs for obesity, depression, and migraine. To resolve the crystal structure of the serotonin receptor, scientists prepared crystals of the receptor[14-15] in a fat gel. With a fresh injection mechanism, they put the gel into the path of LCLS (linac coherent light source) X-ray pulses to gather structural information about the protein. This method tackles the primary challenge in GPCR research: traditional X-ray studies use synchrotron accelerators, which require large crystals, and GPCRS are difficult to reach such sizes.

Through the stimulation of guanine nucleotide exchange in the Gα subunit, G protein-coupled receptors (GPCRS) activate heterotrimeric G proteins[16] . To view this mechanism, a time-resolved cryo-electron microscopy (TEM) approach was devised to investigate the integration of presteady-state intermediates of GPCR-G protein complexes. At brief intervals following the injection of GTP, the transfer of stimulatory G protein to the β2-adrenergic receptor (β2AR) complex was seen via variability analysis. Lastly, the conformational paths of G protein dissociation and activation from receptor activity were identified. A high-resolution depiction of the series of events causing G-protein activation upon GTP binding is given by the 20 transition structures produced by a subset of successively overlapping particles along this pathway, as opposed to the control structure. Structural alterations that propagate from the nucleotide-binding pocket into the GTPase domain weaken the G protein-receptor interaction, affecting the α5 helix and the Gα switch region.

3.3.2 Development of biased allosteric modulators (BAMs)

Allosteric modulators are a class of small molecules that are able to bind to the nonorthomeric sites of GPCRs, and they regulate signaling by changing the conformation of the receptors.

The new field of GPCR drug discovery remains because traditional agonist and antagonist ligands are not always able to achieve receptor isoform selectivity and control off-target and on-target side effects.

Biased allosteric modulators (BAMs) are innovative GPCR ligands that engage with less conserved regulatory motifs beyond the positive constitutive pocket, resulting in pathogen-specific impacts on receptor signaling.By concentrating on the development of allosteric ligands with signaling bias, these challenges can be overcome. The distinct way BAMs construct receptor signaling presents an opportunity to fine-tune physiology and develop safer and more selective therapeutics. Here, the mathematical description of BAMs is explored, along with the challenges and considerations in drug discovery. Although there are challenges, they can be overcome with well-designed drug discovery efforts. The therapeutic advantages of BAMs and recent reports on beta-inhibin bias modulators suggest that such drug discovery efforts will be valuable.

In summary, BAMs may provide novel strategies for GPCR drug discovery, especially in treating neurological diseases. With a deeper understanding of BAMs and technological advances, BAMs are expected to become an important direction for future drug development.

3.3.3 Application of gene editing technology in the study of GPCRs

Using CRISPR/Cas9 and other gene editing technologies to precisely modify GPCRs genes, we can study their mechanism of action under physiological and pathological conditions.

These technologies allow researchers[18] to site-directed insertion of unnatural amino acids (Uaa) carrying light-sensitive groups into GPCRs, thereby converting these light-insensitive proteins into novel photoreceptor proteins. These modified GPCRs can respond to light signals through photocaging, photocross-linking or photoisomerization, providing a new tool for studying the role of GPCRs under physiological and pathological conditions. In addition, the application of CRISPR/Cas9 technology has also been extended to create a library of GPCRs mutants in model organisms, which provides rich experimental materials for drug screening and verification, and further promotes the in-depth understanding of the mechanism of GPCRs in nervous system diseases.

3.3.4 Application of artificial intelligence and machine learning in drug discovery

A large-scale GPCRs database and drug molecule library were constructed, and machine learning algorithms were used for data mining and pattern recognition.

Through these technical means, potential drug candidates can be quickly screened, and the structure and properties of drug molecules can be optimized.

This innovative strategy is expected to improve the efficiency and success rate of drug research and development, and accelerate the process of new drugs to market.

With the continuous progress of science and technology and the in-depth interdisciplinary cooperation, innovative strategies for drug development of GPCRs will continue to emerge. These strategies will not only help to improve the specificity, efficacy and safety of drugs, but also provide new hope for the treatment of nervous system diseases and other related diseases. In the future, we can expect more innovative GPCRs drugs to come out and make greater contributions to human health.

4 Future research directions and challenges

Future research will continue to explore the specific mechanisms of GPCRs in neurological diseases, discover new drug targets, and develop drugs with higher selectivity, better tolerance, and better efficacy. The intersection of structural biology, computational biology, and pharmacology will provide new tools and approaches for GPCR drug discovery. Clinical studies will continue to validate the safety and efficacy of GPCR drugs and provide more treatment options for patients.

In conclusion, GPCRs have a broad application prospect in the management of neurological disorders.With the further understanding of the function and regulatory mechanism of GPCRs, we are expected to develop more targeted therapeutic drugs with good efficacy and few side effects, which will bring new hope to patients with neurological diseases.

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