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Glutamate Receptor Modulation as a Therapeutic Strategy in Neuro-degenerative Diseases: Mechanisms, Pharmacological Targets, and Fu-ture Perspectives

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ABSTRACT

Glutamate is the principal excitatory neurotransmitter in the central nervous system and plays a crucial role in synaptic transmission, neuronal development, memory formation, and synaptic plasticity. However, dysregulation of glutamatergic signaling can lead to excitotoxicity, a pathological process characterized by excessive calcium influx, oxidative stress, mitochondrial dysfunction, and neuronal damage. This mechanism has been strongly implicated in the pathogenesis of several neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Glutamate receptors are broadly classified into ionotropic receptors (NMDA, AMPA, and kainate) and metabotropic glutamate receptors, both of which play essential roles in neuronal communication. Pharmacological modulation of these receptors using antagonists, agonists, and allosteric modulators has shown promising neuroprotective and disease-modifying effects in experimental studies. Nevertheless, clinical translation remains limited due to issues related to receptor selectivity, adverse effects, and incomplete understanding of glutamatergic pathways. Future research focusing on receptor subtype–selective modulators, improved safety profiles, and personalized therapeutic approaches may enhance the clinical potential of glutamate receptor–targeted therapies.

Keywords: Alzheimer's disease; Amyotrophic lateral sclerosis; Excitotoxicity; Glutamate; Glutamate receptors; Neurodegeneration; NMDA receptors; Oxidative stress; Parkinson's disease; Synaptic plasticity.

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INTRODUCTION

Glutamate is the principal excitatory neurotransmitter in the central nervous system (CNS) and plays a critical role in synaptic transmission, neuronal development, memory formation and synaptic plasticity [1]. Nonetheless, the deregulation of the glutamate signaling pathway may cause the overstimulation of neurons which cause neuronal dysfunction and cell death. This is the excitotoxicity pathophysiological pathway, and it is believed to be one of the major mechanisms that contribute to a broad range of neurodegenerative diseases [2]. Excitotoxicity results from excessive activation of glutamate receptors, leading to increased Ca^{2+} influx, oxidative stress, mitochondrial dysfunction, and neuronal injury [3]. Glutamate acts on two broad categories of receptors which are: ionotropic glutamate receptors and metabotropic glutamate receptors. The ionotropic receptors facilitate fast synapse transmission and the metabotropic glutamate receptors control slower modulatory signaling. Inhibition of these receptors through pharmacological means has proved to be a promising treatment option. Although, there exist numerous publications in the literature providing solid neuroprotective and disease-modifying effects

of various glutamate receptor modulators, such as agonists, antagonists, and allosteric modulators, in a few experimental models of neurodegeneration the application of such information into clinical therapy remains very low [2] .Importantly, the pathogenic role of glutamate-mediated excitotoxicity in several neurodegenerative disease models has been repeatedly confirmed by numerous glutamate receptor modulators including agonists, antagonists. There are 8 metabotropic glutamate receptor subtypes: mGluR1–mGluR8, classified into three groups in **Table 1.**

Table 1: metabotropic glutamate receptor subtypes

Group	Receptors	Function
I	mGluR1, mGluR5	excitatory
II	mGluR2, mGluR3	inhibitory
III	mGluR4, 6, 7, 8	inhibitory

Glutamate Neurotransmission in the Central Nervous System

The key excitatory neurotransmitter in the central nervous system (CNS) is glutamate which is a key component of neuronal communication. It facilitates fast synaptic transmission via ionotropic glutamate receptors as well as controls slower, long-term cellular and metabolic effects via metabotropic glutamate receptors. The role of glutamate in brain processes has received some critical attention as some studies have indicated that glutamate is important in the processes of cognition and the formation of memories [4,5]. The glutamate receptors known as the ionotropic glutamate receptors (NMDA receptor, AMPA receptor and Kainate receptor) are critical in fast excitatory transmissions and neuronal excitability and synaptic activities. As an example, it has been well established that glutamatergic signaling can cause memory formation, neuronal development, and higher cognitive processes [6,7]. It is therefore important that extracellular glutamate levels should be regulated properly to ensure neuronal homeostasis. Glutamate transporters are very important in this process as they quickly remove the unnecessary neurotransmitter in the cleft and maintain the extracellular levels at low levels and hence avoid neurotoxicity [8]. In physiological conditions, the amount of extrasynaptic glutamate is closely regulated to prevent excessive stimulation of glutamate receptors [4]. The glutamatergic synapse is therefore held in a robust consensus by a large number of high citation reviews on the importance of glutamate signaling in the healthy functioning of the CNS and how impairment of this highly regulated system may play a role in the occurrence of neurological and neurodegenerative disorders.

Types of Glutamate Receptors

The two major types of the receptors in this category of glutamate reuptakers are ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs), which are mostly divided in terms of structure and mechanism of action. The ionotropic receptors transduce fast synaptic messages through the use of ligand-gated ion channels and the metabotropic receptors through the use of G-protein-mediated intracellular signals [10]. The two types of receptors have a combined role in the excitatory neurotransmission which forms the center of the neuronal communication and synaptic plasticity. These ion channels are ligand-gated receptors; structurally, the receptors are tetrameric subunits which form cation selective pores through which ions like NA+, K+ and Ca2+ can pass through the neuronal membrane [11]. Of the subtypes, NMDA receptors differ in terms of their functional properties, including the requirement of co-agonist binding of glutamate and glycine and voltage-dependent Mg2+ block that regulates the opening of ion channels. In addition to this, the NMDA receptors are very permeable to Ca2+ ions and this is necessary in intra cellular signaling pathway which are involved in the synaptic plasticity and neuronal development. To the contrary AMPA and kainate receptors significantly contribute to the fast excitatory transmission of the synapses, and are constituted of variable subunit combinations that define the activities of these receptors.The activation requirement of kainate receptors is also unique because the optimal operation of the receptors requires the presence of extracellular Na+ and Cl- ions [11]. Another important group of glutamate receptors is the metabotropic glutamate receptors which is part of the family C group of G-protein-coupled receptors. In contrast to ionotropic receptors, mGluRs do not directly form ion channels; rather they regulate neuronal activity by means of intracellular signaling pathways that can regulate synaptic transmission, neuronal excitability, and neurotransmitter release [10]. All types of receptors have different synaptic localization. Ionotropic receptors are mainly located at the synaptic core, which mediates fast postsynaptic responses whereas metabotropic receptors are usually located at the periphery of synapses, which enables them to modify the synaptic activities over a longer period of time [13]. The recent research has continued to enlarge the knowledge on the glutamate receptor signaling. Recent evidence indicates that the ionotropic glutamate receptors also can be involved into flux-independent signaling pathways, where the activation of the receptors promotes intracellular processes without involving ion flow through the channel pore. The discovery makes the glutamatergic signaling more complex and hints at the possibility of even more mechanisms through which the glutamate receptors can play a role in neuronal functioning and pathophysiology.

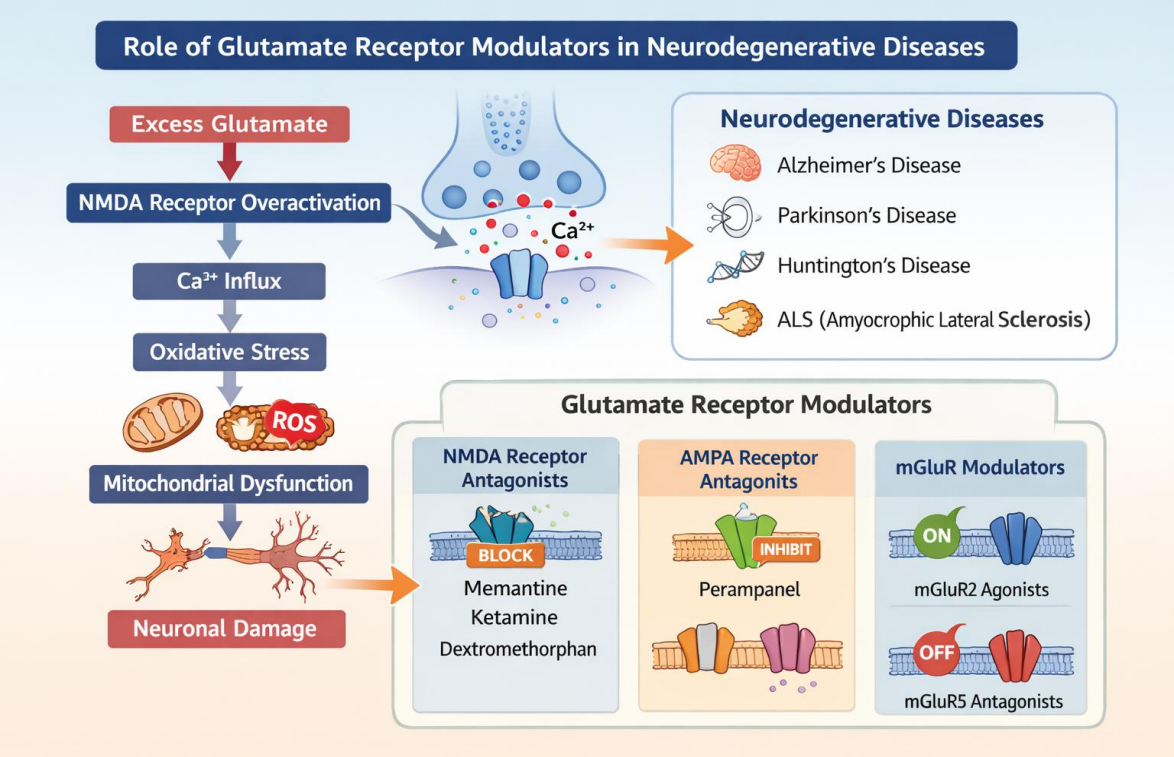

Figure 1: Mechanism of glutamate-mediated excitotoxicity and therapeutic targets of glutamate receptor modulators in neurodegenerative diseases.

Glutamate Receptors in Neurodegenerative Diseases

Glutamate receptor dys-regulation was strongly implied as a pathogenesisic agent in a number of numerous neurodegenerative diseases such as Alzheimer disease, Parkinson disease, Huntington disease and Amyotrophic lateral sclerosis. Evidence This disease pathogenesis. The role of excitotoxicity mediated by glutamate as central pathogenic mechanism in a number of neurodegenerative disorders, especially in the case of Alzheimer disease, Huntington disease and amyotrophic lateral sclerosis, was clearly stated to have a long and long-standing history of both foundation and review articles [14]. To provide an example, preclinical trials between 2022 and 2025 have shown that mGlu5 receptor and group III metabotropic glutamate receptors play a large role in these neurodegenerative diseases and thus these two types of receptors could serve as effective pharmacological targets [15]. The therapeutic potential of glutamate receptor modulation is also clinically supported. Memantine, an NMDA receptor antagonist, is now approved in the treatment of moderate to severe Alzheimer dementia and is one of the limited clinically-verified treatments aimed at treating the glutamatergic dysfunction [16]. Although there have been promising results with improving experimental models, translation of emerging glutamate receptor modulators into effective clinical therapies has been limited. Specifically, limited clinical trial data on metabotropic glutamate receptor targeted drugs have been published in other areas of neurodegenerative disease and not yet in Parkinson disease. Further investigation is thus required so as to have more knowledge of the therapeutic potential and clinical practicability of glutamate receptor-targeted interventions. Excessive glutamate release leads to overactivation of glutamate receptors, particularly NMDA receptors, resulting in Ca^{2+} influx, oxidative stress, mitochondrial dysfunction, and neuronal damage. The major pathways involved in glutamate-mediated excitotoxicity and the potential pharmacological targets of glutamate receptor modulators are illustrated in **Figure 1.**

Pharmacological Modulation of Glutamate Receptors

GRMs have become a valuable treatment approach in the treatment of numerous neurological and psychiatric conditions. These drugs are focused on various subtypes of glutamate receptors, aiming to control the excitatory neurotransmission and avoid the damage to neurons, which is pathological. Of these, the most clinical interest has been given to modulators of the NMDA receptors, which are closely linked to excitotoxic neuronal damage in cases of excessive activation of NMDA receptors. At the moment, the NMDA receptor antagonist Memantine is the sole medication of this type that is now approved to be used in clinical practice, especially with the treatment of moderate-severe cases of Alzheimer. Memantine is an uncompetitive NMDA receptor antagonist that is safe and well-tolerated and assists in controlling pathological glutamate functions without disrupting normal physiological

signalling [16]. Some other NMDA receptor antagonists besides memantine have also been researched due to their therapeutic potential. Other drugs that have been studied to treat mood disorders, especially the Major depressive disorder are Ketamine, Dextromethorphan and AZD6765. Ketamine has been one of the most effective and fastest antidepressants of this group and its structurally related agents have shown less impressive results in therapy. In addition to NMDA receptor antagonists, other glutamate receptor subtypes also have modulators that have demonstrated good results in the experimental and preclinical studies. The AMPA receptor is also undergoing positive allosteric modulators as a possible cognitive enhancer because of their capacity to enhance synaptic plasticity and learning. Likewise, there has been growing interest in pharmacological agents which are directed at the metabotropic glutamate receptors. The mGluR2 agonists are tested on the implementation of their potential anxiolytic action, and the mGluR5 antagonists are also tested to be potentially applicable to the treatment of anxiety disorders, chronic pain, and substance abuse [17]. Later research has broadened the range of clinical applications of modulators of glutamate receptors to include a broader range of neurological and psychiatric disorders. The glutamatergic targets have been discovered to play a role in, among others, such diseases as Schizophrenia, depression, addiction, and other forms of neurodegenerative disorders [18]. Although these results are encouraging, there is poor translation of most of the glutamate receptor modulators in the preclinical studies into therapeutic interventions. Most other drugs targeting the glutamate receptor, including the glutamate NMDA receptors, are still in the research phase, with the observation that more clinical trials are necessary to confirm their therapeutic value.

Current Pharmacological Therapies Targeting Glutamate Receptors

Although glutamatergic signaling is increasingly recognized as a cause of neuromicrosomia, few drugs that directly interact with glutamate receptors are currently approved to be used in the treatment of neurological disorders. An example of such one is Perampanel which is currently permitted to treat focal epilepsy. Perampanel is a selective AMPA receptor antagonist and is one of the few commercial drugs that have the potential to alter the activity of glutamate receptors; nonetheless, the effects of such drugs on the body are more complex than direct action on the receptor.Many other glutamate receptor modulators have already entered clinical trials, and these drugs have multicomponent effects on the body in addition to affecting the receptor. A number of compounds that focus on NMDA receptor have been assessed on the basis of their possible therapeutic value which include Ketamine, Memantine, Dextromethorphan and AZD6765. Moreover, NR2B-subunit receptor subtype selective antagonists including CP-101,606 and MK-0657 have been investigated in the clinical trials. Glycine-site partial agonists, including D-cycloserine and GLYX-13, and metabotropic glutamate receptor modulators, including AZD2066 and basimglurant, are also other pharmacological interventions. Among them ketamine has shown quick antidepressant characteristics in individuals with treatment resistant condition, and GLYX-13 has exhibited encouraging therapeutic impacts as a monotherapy in preclinical trials [20]. Nevertheless, clinical development of glutamate receptor modulators has had a number of challenges. Among the most significant limitations, the development of negative consequences of excessive inhibition of the glutamatergic signaling can be identified. Cognitive and psychotomimetic symptoms have also been widely reported with some NMDA receptor antagonists which makes them hard to use therapeutically [21]. Moreover, not all NMDA antagonists have been linked with side effects, which is why they have not been extensively used in clinical practice [22]. Consequently, recent studies are drifting towards the development of receptor-subtype selective modulators and allosteric compounds, which can bring therapeutic effects and at the same time reduce the adverse effects. Recent advances in targeted and cell-based therapies further demonstrate the growing importance of personalized therapeutic strategies in modern biomedical research. For instance, innovative immunotherapeutic approaches such as chimeric antigen receptor T-cell (CAR-T) therapy have significantly improved treatment outcomes in hematological malignancies, particularly pediatric acute lymphoblastic leukemia [24]. Although such therapies are primarily used in oncology, the concept of highly specific molecular targeting highlights the broader potential of precision-based therapeutic approaches that could also influence the development of future glutamate receptor-targeted therapies in neurological disorders. Pharmacological modulators of glutamate receptors and their therapeutic applications is mentioned in **Table 2.**

Table 2: Pharmacological modulators of glutamate receptors and their therapeutic applications

Drug	Target receptor	Indication
Memantine	NMDA antagonist	Alzheimer's disease
Ketamine	NMDA antagonist	Depression
Perampanel	AMPA antagonist	Epilepsy

Challenges and Future Perspectives

There has been a significant therapeutic potential of the use of glutamate receptor modulators in the

treatment of neurodegenerative diseases. Nevertheless, there are still a number of issues to overcome and among the key challenges, there is the issue of sufficient selectivity with a minimum of adverse effects. As stated [22], NMDA receptor antagonists exhibit potential therapy in neurological disorders, but cannot be used in clinical practice because of severe side effects at therapeutic doses. This brought about the necessity of the development of receptor subtype selective compounds that have the capacity of maintaining efficacy without increasing toxicity. Nevertheless, the development of novel glutamate receptor modulators has improved dramatically [17] has also reported that despite the growing number of group III metabotropic glutamate receptor (mGluR)-selective ligands, future studies need to emphasize the development of novel ligands with greater activity and better safety profiles. More recently, [15] reported that the newly developed allosteric modulators have shown the ability to improve cognitive performance and decrease the pathology of the disease in preclinical models with promising therapeutic potential.The current literature offers little direct evidence proving the individualized approach to pharmacotherapy with glutamate receptor modulators. However, recent progress of receptor subtype-selective agents suggests a shift in the new direction of using more specific and possibly even customized therapeutic options in the treatment of neurodegenerative disorders. Recent advances in immunology and precision medicine have significantly influenced the development of targeted therapeutic strategies for complex diseases. Precision-based approaches integrate molecular biomarkers, genetic profiling, and individualized treatment strategies to improve therapeutic outcomes in chronic disorders. For example, the integration of immunological mechanisms with precision medicine has been shown to improve therapeutic strategies in inflammatory disorders such as rheumatoid arthritis, highlighting the importance of individualized treatment approaches in modern medicine [23]. Similar concepts may be applicable to neurodegenerative diseases, where glutamate receptor modulators could be optimized through biomarker-guided therapeutic strategies.

CONCLUSION

Comprehensive clinical reviews of rare genetic disorders have also emphasized the importance of multidisciplinary therapeutic strategies and improved molecular understanding for effective disease management [25]. Similar integrative approaches combining pharmacology, molecular biology, and clinical research may contribute to the development of more effective glutamate receptor-based therapies for neurodegenerative diseases.. One of the treatment modes that can be utilized in the management of the neurodegenerative diseases is the glutamate receptor modulators that have the capacity to control the excitatory neurotransmission to counteract the excitotoxicity that glutamate causes. Glutamatergic signalling has been realized to be unregulated and the potent cause of extensive range of neurological illnesses including Alzheimer disease, Parkinson disease, Huntington disease and amyotrophic lateral sclerosis. It is shown that neuroprotective and disease-modifying effects of the pharmacological control of the glutamate receptors i.e. antagonists, agonists and allosteric modulators are observed in numerous experimental and preclinical models.In spite of some positive outcomes, the fact that the list of drugs available is rather scarce, still reflects a number of issues that stand in the way of successful transportation of glutamate receptor modulators to the realm of daily clinical treatment. The key ones are restricted specificity of the receptors, possible adverse effects and insufficient knowledge about the glutamatergic signalling pathways. Hence, receptor subtype-selective compounds and new forms of allosteric modulators that have the ability to offer therapeutic effects but reduce toxicity should be considered in future research. Secondly, there is a need to conduct more extensive clinical trials in order to assess the safety, effectiveness, and long-term effects on the patient with neurodegenerative diseases on these agents. New technological achievements in the field of molecular pharmacology, biomarker identification, and precision medicine could become an additional source of enhancing the personalized glutamate-directed therapy, which would ultimately result in better treatment of those with neurodegenerative disorders.

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Conflict of Interest

The authors declare that there are no conflicts of interest related to this work.

Ethical Approval

Ethical approval was not required for this study, as it is a systematic review based exclusively on previously published data.

Informed Consent

Informed consent was not applicable, as no individual patient data were collected or analyzed in this study.

Data Availability Statement

All data analyzed in this study are included in the published articles identified through the systematic review and are available within the manuscript and its supplementary materials.

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