REVIEW ARTICLE

Pharmacological innovations in psychiatric treatment: exploring novel therapeutic targets

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ABSTRACT

Psychiatric disorders pose frequent treatment challenges thus exploring new treatment modalities is always desirable by the experts in the field. Possible treatment options include medications that can alter or target the glutamatergic system, immunologic system, and/or neuroinflammatory pathways. The efficacy of such systems has been demonstrated in preclinical and clinical trials, mainly in the enhancement of symptoms related to mental disorders. However, questions arise like: Is it feasible to develop the target? Do the emitting pole and the receiving pole indicate that the treatment is the best one? On what basis should the patients be grouped? Assessing such pathogenic mechanisms concerning novel targets will enable the identification of the course toward personalized and patient-tailored medication for a variety of psychiatric ailments. The findings of this narrative literature review may shed light on the new potential therapeutic targets for psychiatric diseases, that may be utilized for better treatment outcomes in the mental healthcare system.

Keywords: Psychiatric illnesses, neuroinflammation, glutamatergic neurotransmission, glutamatergic system.

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Introduction

The most commonly occurring psychiatric disorders like depression, anxiety, schizophrenia, and bipolar disorders significantly affect the patients and their families, alike.[1,2] For this reason, numerous patients find some relief through available treatments such as selective serotonin reuptake inhibitor and antipsychotic medications; however, about half of the patients claim their symptoms receive insufficient remission and are accompanied by significant side effects.[3,4] It is, therefore, essential to bear in mind the quest for new approaches that can help the production of newer therapies for psychiatric diseases.[5,6]

This is because, in the last decade or so, there have been advances in understanding that the glutamatergic system and the immunological system, neuroinflammation per se, may be the other targets of psychopharmacological treatments for psychiatric disorders. Neuronal transmission of the brain's glutamate system (Figure 1) is recognized as one of the most critical systems that plays an essential role. Changes in synaptic plasticity, cognitive difficulties, and mood disorders have also been attributed to glutamatergic dysregulation.[7] Manipulating specific glutamate receptors, such as N-methyl-D-aspartate (NMDA) receptors, is considered as new treatment approach in experimental and clinical research.[1,8]

Furthermore, accumulating evidence is available that shows that immune-mediated activation and processes of neuroinflammation may be implicated in the pathogenesis of mental disorders. For instance, in one study it was found that depressed and schizophrenic patients, or patients with bipolar disorders have increased levels of inflammatory biomarkers like cytokines and chemokines.[10] Recently, more substantial proof has provided bidirectional communication between the peripheral immune system and central nervous system, and studies performed in this work are in approximation to the hypothesis of flipping of immunoinflammatory balance regulating neurotransmission and neuroplasticity in psychiatric disorders. Therefore, the potential area of interest regarding new specific therapies for regulating immunological modifications should be highlighted.[11,12] This review aims to explain the new targets found in the neuroinflammatory mechanisms and glutamate

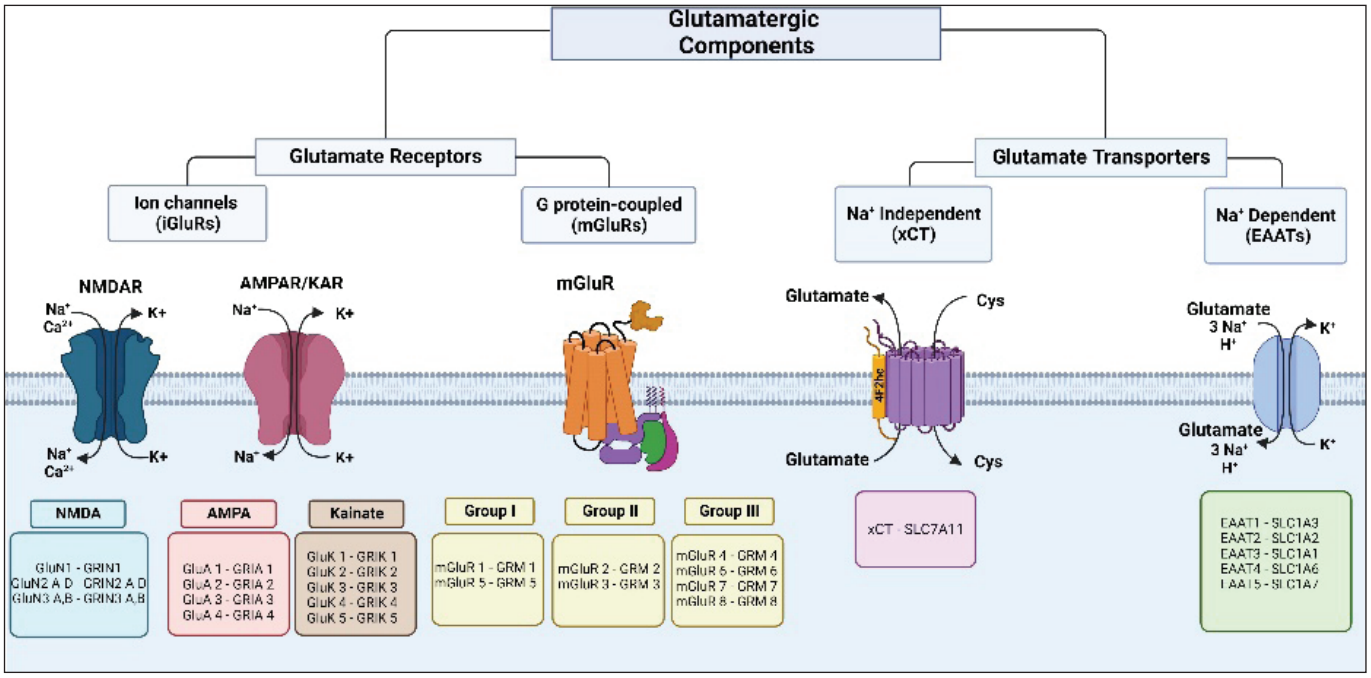

Figure 1. *Classification of glutamate receptors and transporters. The left panel shows iGluR subunits and the respective coding genes. In the middle, the proteins and respective coding genes of mGluR families are shown. The right panel shows glutamate transporters of glutamate efflux and influx. Cys, cysteine.*[9]

system to explore novel treatments for psychiatric disorders that positively impact patients' outcomes and fulfill unmet needs in their mental health.

Methods

This literature review encompasses articles available on MEDLINE/PubMed from the year 2019 onwards. The search terms utilized were "psychotropic drugs", "novel" "psychiatry therapeutics", "neuroprotective agents", and "mental disorders". The inclusion criteria comprised original articles, systematic reviews, or review articles involving adults and adolescents diagnosed with psychiatric disorders such as depression, anxiety, schizophrenia, or bipolar disorder. Conversely, studies that focused exclusively on pediatric populations (children under 12 years) or conditions unrelated to psychiatric disorders and Editorials, commentaries, or opinion papers were excluded.

Discussion

In such targets of interest to enhance the efficacy within the pharmacological treatment of mental disorders, the further potential of the therapeutic targets coordinated in the glutamate transmission immunology and neuroinflammatory system is pivotal.[5] More research is needed concerning how the approaches mentioned above can be developed to treat these organizations and the processes to demonstrate the efficacy and safety of the interventions for the new forms of these pathways.[1] Possibly, the efforts to invest in the timely improvement in the patients' outcomes, the decrease in the level of non-compliance to the currently available treatments, and the cost-effectiveness will be the possible factors leading to the acceptability of these new types of treatments.[6,10]

Multiple mental disorders have been proven to relate to the glutamatergic signaling systems. Therefore, the condition and treatment of the affected patients require intentionally directed attention on this particular system. Currently, preliminary data from the level of basic research shows the potential for intervention or molecular targeting of this neurotransmitter, especially with the NMDA receptor, and the possibility of attenuating symptoms associated with psychiatric diseases.[1,8] However, new-generation glutamatergic drugs, including metabotropic glutamate receptor agonists and agonist and antagonist treatments for NMDA receptors, will be under thorough investigation. These therapeutic targets ensure the limits of the excitatory processes in the nervous system, increase the production of neurons, and mend the strength of the connection between the neurons.[6] Furthermore, the pro-inflammatory cytokines, including the IL-6 and tumor necrosis factor-alpha, have been found to have higher concentrations in depressed, schizophrenic, and bipolar individuals.[11] Free radicals and inflammatory biomarkers participate in the immunological cross-talk within or concerning signaling controls; hence, anti-inflammatory agents/immune system modulators may

be explicitly incorporated to probably alter immunological phenotypes and thereby reduce or eliminate the prospect of depression and other psychotic-like features accompanied by better treatment outcomes. For instance, given that the immune system can interact with the brain and that psychiatric disorders are no longer viewed as unidimensional and multifaceted diseases, the clinician is faced with the difficult task of deciding which immunomodulation approach may have the best chance of paying off or what specific patient population may profit from immunomodulation therapy.[12,13]

The nature of psychiatric diseases as dynamic multifactorial conditions may necessitate the many-target approach since this would correspond to complementary cross-interactions contributing positively to the progress of the therapeutic procedure.[5] Combining therapy implies that immunological disorders are being treated with immunomodulatory drugs that are used at the same time as glutamatergic drugs for the treatment of neuronal dysfunction in persons with psychiatric diseases.[8] Nevertheless, further fundamental research and controlled clinical study of the medicine's merits and demerits are required to elucidate the possible benefits of combination medicines that target these newly identified receptors.[14]

Although NMDA receptor antagonists have been demonstrated to possess antidepressant-like activity, the molecular changes underlying abnormal glutamatergic signaling still remain poorly understood. A growing number of studies support the use of memantine and minocycline in major depressive disorder and schizophrenia. Amantadine, zinc, and *Crocus sativus* extracts yield the potential to ameliorate depressive symptoms in patients with affective disorders. However, the benefits and drawbacks can certainly be outlined when introducing these new targets for glutamatergic systems.[11] First, these targets are closely related to psychiatric diseases, their phenomenology, and the possibilities of their pharmacological modulation using significant preclinical studies for their discovery and validation.[1] However, for a detailed understanding of the possible application of glutamatergic system-related therapies, it should be supported by large-scale clinical trials that reveal the effectiveness, side effects, and toxicity profile in patients and elaborate on mechanisms that determine the interaction between new targets and therapies in the local population.[4] Some modern medical approaches such as biomarkers, identification of particular sets of biological markers, and creation of disease, treatment, and therapy protocols.[14] In particular, local sub-populations with psychiatric symptoms can also help formulate treatment programs that may apply to our specific sub-groups of the populace.

Limitations of the Review

The review is of a narrative nature and hence lacks the systematic analysis of literature and scientific evidence. Further molecular basis of pathogenesis and target drug therapy have not been discussed. The data retrieved are from the past 5 years (2019-2024).

Conclusion

Finding new treatments for psychiatric disorders has brought much hope through studies in the glutamatergic system and immunological systems. Large-scale studies and clinical trials nevertheless necessitate further research to explore an in-depth mechanism of action of these targets, enhance the treatment methods, and identify the right patients' group for personalized therapy.

List of Abbreviations

IL-6	Interleukin 6
NMDA	N-methyl-D-aspartate

Conflict of interest

None to declare.

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Ethical approval

Not required.

Authors' contributions

MA: Concept and design of the study, drafted the manuscript, critical revision, and analysis

UV: Critical revision and drafting the manuscript, acquisition of data

ALL AUTHORS: Approval and responsibility of the final version of the manuscript to be published.

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