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From Glutamatergic Dysfunction to Cognitive Impairment: Boundaries in the Therapeutic of the Schizophrenia

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Abstract: Cognitive deficits are trait markers in schizophrenia and the improvement of these dysfunctions has been considered as a new frontier of treatment in this disease. A current model for the patophysiology of schizophrenia states that N-methyl-D-aspartate receptor (NMDA) hypofunction leads to a dysregulation of gamma-amino butyric acid (GABA) fast- spiking interneurons, consequently disinhibiting pyramidal glutamatergic output and disturbing signal-to-noise ratio. In this way, the modulation of the glutamate activity might constitute a highly promising target for future therapeutic interventions of this disease. In the present review, we discuss key regulatory elements for glutamatergic neurotransmission and provide new insights into their potential role in developing pharmacological treatments. Also, we emphasize the role of certain chemical families as potential sources of new lead compounds with affinity for metabotropic glutamate receptors (mGluRs) with cognitive enhancing properties.

Keywords: Schizophrenia treatment, Cognitive deficits (CDs), N-methyl-D-aspartate receptor (NMDAR), Astrocytes, Glutamatergic hypothesis, Metabotropic glutamate receptors (mGluRs), Glycine trasporters, Kynurenic acid (KYNA).

INTRODUCTION (AND OVERVIEW)

Although schizophrenia (SZ) has classically been characterized by the "positive" symptoms (e.g. hallucinations, delusions and thought disorder), recent research has highlighted the importance of cognitive deficits (CDs) in this disease. The CDs include alterations in attention, semantic and explicit memory, working memory and executive processes [1]. Unlike the positive symptoms, CDs are present in high-risk population for SZ and remain stable during the course of the disease [2, 3]. Moreover, CDs are more severe in SZ than in others psychiatric diseases (e.g. bipolar disorders, depression or drug abuse) [*3*]. Working memory (WM) alterations have been considered as one of the core cognitive symptoms in SZ [4]. WM refers to a cognitive process that actively hold and manipulate information in the brain for subsequent immediate processing [5]. WM dysfunctions are key factors of the detriment of functional outcome and long term prognosis of personal and social interactions in SZ patients [6]. Moreover, the fact that close relatives of SZ patients show similar WM alterations and are consistently present during all the stages of the disease, has led to consider the WM dysfunctions as a trait marker in SZ [7]. Thus, the development of new therapeutic strategies that significantly improve CDs has become one of the most important challenges in the therapeutics of SZ.

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To understand the role of potential new pharmacological treatments in SZ, it is necessary to overview the molecular mechanisms underlying CDs in SZ. In this sense, although a wide range of molecular pathways have been associated with the WM process and SZ, we will mainly focus on the Glutamatergic and GABAergic system, because the currently available antipsychotic medication targeting other systems, such as the Dopamine system, have yielded only mild improvement of CDs [8]. A possible pathophysiological framework has been recently stated in the following manner: a failure in the establishment of cortico-cortical networks during development of the brain could compromise migration of Gamma-amino-butyric (GABA)-ergic neurons, and thus disrupt the cortical tuning of the Glutamatergic pyramidal neurons. This, in turn, may provoke a disengagement of the cortical ongoing- and driven- neuronal local field potential in the brain through some mechanisms that are still under debate [9]. Thus, the study of the modulation of glutamatergic neurotransmission is relevant in the development of new pharmacological treatments and we will review the evidence that supports the glutamate hypothesis in SZ.

Although new molecules than modulate the glutamatergic excitatory output have been previously studied, fewer studies have focused on how the modulation of this output by related networks is affected. For example, astrocytes play a key role in the synaptic metabolism of glutamate and monamines, and astrocyte dysfunction may well be related to the physiopathology of SZ through the mechanism explained above [10]. Thus, the second goal of this review is to point out the importance of astrocytes in the regulation of glutamate and to remark their importance as potential therapeutic

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targets for the improvement of CDs in SZ. The third part of the present work will be dedicated to the discussion of new disease-modifying molecules emphasizing the role of certain chemical families as sources of lead compounds targeting, through the metabotropic modulation of N-methyl-D-aspartate receptor (NMDAR).

EVIDENCE OF GLUTAMATERGIC HYPOTHESIS AND ITS IMPLICATIONS IN THE COGNITIVE DEFICITS IN SCHIZOPHRENIA

The glutamatergic hypothesis in SZ has been extensively studied and evidence in favor it is constantly growing. This hypothesis states that the hypofunction in glutamatergic cortical receptors (mainly NMDAR) is the core alteration in the physiopathology in the disease [11, 12]. One of the first pieces of evidence in support of this hypothesis was the observation that Phencyclidine (a non - competitive NMDAR antagonist) closely mimics positive, negative and cognitive symptoms observed in SZ [13]. Afterwards the same effect was observed using other NMDAR antagonists, such as MK-801 and Ketamine [14, 15]. Besides, these molecules worsen positive symptoms in chronic- and non- medicated patients [16] and it has been observed that subanesthetic doses of Ketamine correlate with impaired performance on several tasks that evaluate functioning in the cognitive domain [17]. Thus, NMDAR appears to have a relevant role on the whole clinical spectrum of the disease.

Furthermore, drugs that selectively target glutamatergic receptors improve the clinical state of patients even more efficaciously than drugs that selectively target the monoaminergic system [18, 19]. At a genetic level, a severe decrease of the transcripts of genes related to glutamatergic neurotransmission has been consistently observed in SZ by using DNA microarray technique [20, 21]. At a systemic level, functional neuroimaging and electroencephalogram techniques provide robust evidence of dysregulation of glutamatergic pathways in SZ patients [22, 23]. A relatively recent imaging technique, magnetic resonance spectroscopy, provides a method of studying brain chemistry and cellular features in vivo, including components of the glutamatergic and GABAergic pathways. Other finding that supports the notion of the glutamatergic involvement in SZ is the increase in the concentration of glutamate in the prefrontal cortex and hippocampus of SZ patients [23]. Furthermore, a more recent study shows an association between the neurochemical imbalances and the specific CDs in SZ patients [24].

In summary, the currently available clinical, physiological and genetic evidence, points towards disturbances of the glutamatergic neurotransmission as one of the most reliable neurochemical hypothesis to explain the widespread clinical manifestations of SZ [25]. Taking this evidence into account, the search for new therapeutic strategies that target glutamate receptors becomes critical based on the importance of glutamate alterations in the pathophysiology of SZ and its relation with SZ-related cognitive dysfunctions.

Alterations in Fast- spiking -parvalbumin GABAergic (GABA-FS) interneurons might link Glutamatergic dysfunctions to WM alterations in SZ [26]. Working memory strongly depends on the sustain firing of a subtype of the Glutamatergic pyramidal neurons situated on the Dorsolateral Prefrontal cortex (DLPFC). GABA-FS interneuron finely modulates the firing rate of the Glutamatergic pyramidal neurons output by an inhibitory mechanism [27, 28]. Also, GABA-FS neuron-mediated inhibition is crucial for the mechanisms underlying synchronization of neuronal activity in normal conditions [29].

Although consistent evidence argues that the core alteration of the WM alterations observed in SZ takes place in these neurons, it is still unknown which mechanisms are involved [30]. It has been suggested that alterations in the signaling pathways of the Glutamatergic receptors situated in the soma of the GABA-FS interneuron (AMPA/Kainate and NMDA) might provoke a disengage between the GABAergic-FS interneuron and the glutamatergic pyramidal neurons [31]. Also, the glutamatergic alteration might contribute to the aberrant neuronal activity in the WM networks of SZ patients through the disruption of high- frequency brain oscillations [9, 32, 33] and these impairments might explain perceptual, speech and other cognitive alterations [34, 35].

The explanatory theories about SZ focused initially on the dopaminergic system because of the D2-receptor blocking drugs effect. Substantial evidence has accumulated in the last decades and continues to grow in the present supporting the existence of a dopaminergic dysfunction in SZ. This evidence started to be gathered as clinical and empirical observations and later on more directed approaches started to be broadly used. This conceptual framework offers a direct relationship to symptoms and their treatment [36, 37]. However, as early as in the '70s decade, Carlsson suggested that other transmitters may also be involved in SZ pathogenesis [38]. Today, more is known about the interaction between dopamine and glutamate, and it is widely known that dysregulation of both systems contributes to the occurrence of the disorder in a self-perpetuating complex interaction. Thus, a hierarchical organization of both hypothesis ranking one of them as primary and the other as secondary may be oversimplistic [39]. Furthermore, based on the differential effect of pharmacological interventions modulating dopaminergic system and those modifying NMDAR function, some authors have proposed that dysregulation of these two neurotransmitter systems is involved in different features of the disorder, associating dopaminergic dysfunction with positive symptoms, and glutamatergic dysfunction with negative symptoms, among them CDs [40].

MODULATION OF GLUTAMATERGIC RECEPTORS BY GLIAL CELLS AND THE SEARCH FOR NEW TREATMENTS IN SCHIZOPHRENIA

Glutamatergic neurotransmission imbalance in SZ is certainly a complex phenomenon arising from different mechanisms which at present are not fully understood. Therefore therapeutic strategies aimed at restoring this system may address more than one molecular mechanism. In the following paragraphs we review key regulatory elements for the glutamatergic neurotransmission providing insights into their potential role in novel pharmacological interventions.

Glutamatergic neurotransmission is finely modulated by the activity of astrocytes through different processes. glycine

and D-serine levels are one of the most important modulators of glutamatergic NMDAR through its action on a positive modulatory site on the receptor [41], therefore the use of glycine or glycine agonists has been suggested as a coadjuvant to antipsychotics. In fact, clinical benefits have been encountered in small clinical trials using this approach. The results are less promising for the partial agonist D-cycloserine [41]. Direct administration of these compounds is not the only way to address this system. Brain glycine availability is determined by glycine transporters, especially GlyT-1, which mediates glycine re-uptake into nerve terminals (see fig. (**1**)). GlyT-1 and Glycine trasporter 3 (GlyT-3) exert their action in the soma of astrocytes close to the glutamatergic synaptic. The GlyTs mediate the uptake of glycine in the synaptic cleft. The inhibition of GlyTs modulates the NMDA receptors by switching the glycine availability in the synaptic cleft. Therefore, new therapeutic agents targeting GlyT inhibitors may offer a powerful tool to improve clinical manifestations of SZ patients. In fact, preclinical studies show that chemical GlytT-modulators efficaciously increase CNS glycine levels and reverse the behavioral effects of NMDA antagonists in animals.

It has been proposed that astrocytes are directly involved in synaptic physiology, by integrating and processing synaptic information and finally regulating synaptic transmission and plasticity through the release of gliotransmitters (i.e. transmitters released by glial cells implicated in rapid glial–neuron and glial–glial communication) [42]. The release of this chemical transmitter occurs following an elevation of glial internal Ca2+ concentration in response to neuronal activity. In turn, it causes feedback regulation of neuronal activity and synaptic strength, as well as inter-astrocytic signaling [43, 44]. Gliotransmitters include glutamate [45] D-serine, ATP, homocysteic acid, taurine, atrial natriuretic factor and tumor necrosis factor-alfa (TNF-α) [43]. This interaction is known as the "tripartite synapsis" (TS), has been supported by strong experimental evidence [46], though there is still controversy among different authors [42]. The TS suggest a direct participation of astrocytes in synapsis and the central role of glutamatergic neurotransmission in synaptic transmission, and synaptic plasticity, dysfunctions of tripartite synapsis have been proposed as mechanisms involved in the clinical features of SZ [43, 47]. The restoration of this system may be one of the mechanisms that explain the effect of compounds acting on mGluRs. In fact, astrocytes express all subtypes of mGluRs [48].

Astrocytes also have a key role in the glutamatergic synapsis by another mechanism: they regulate the uptake of glutamate released by neurons through specialized transporters. After glutamate is uptaken, it is then converted to glutamine by the enzyme Glutamine synthetase. Glutamine is subsequently cycled back into neurons. Thus, along with producing the recycling of the transmitter this process allows the maintenance of the spatial and temporal specificity of the neurochemical signal [49]. An effective antipsychotic drug, clozapine, has been proven to induce down-regulation of glutamate transporter - 1 in rat cerebral cortex, providing a possible explanation of its clinical effect [50].

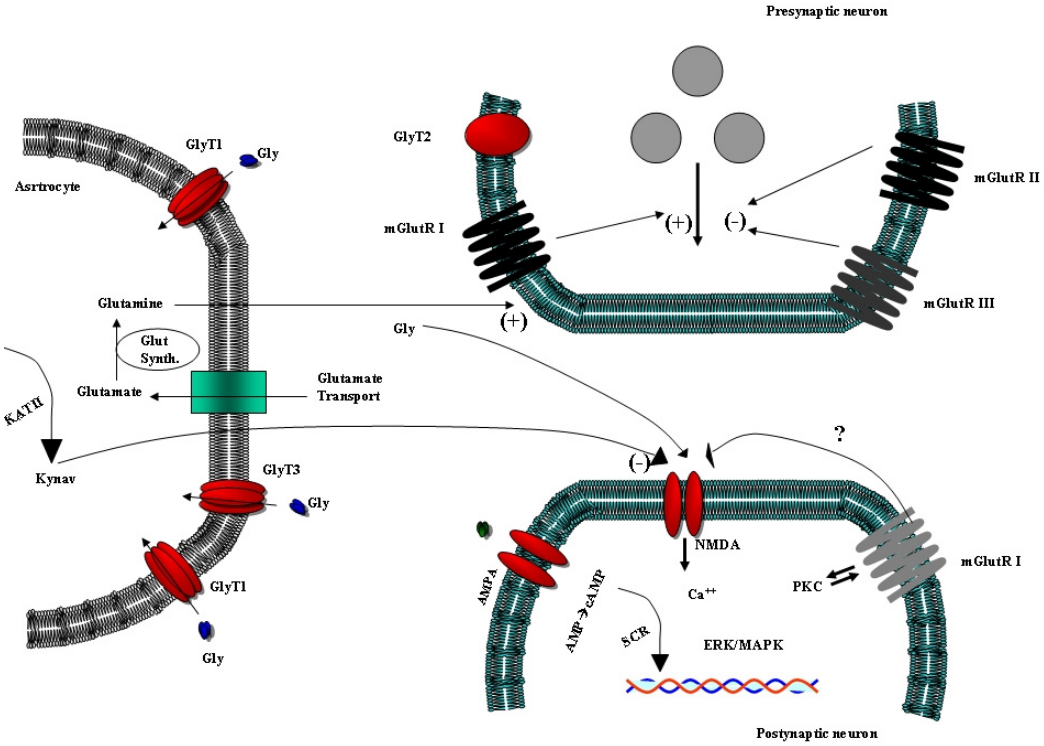

Fig. (1). The glutamatergic neurotransmission in schizophrenia. The NMDA receptor is modulated by metabotropic and ionotropic receptors. Also, the NMDAR is subtly regulated by levels of Glycine (Gly), Kynurenic acid (KYNA) and glutamate through specific receptors situated in the membranes of the Astrocytes. Impairments in the regulation of the mGLURs agonists and Glycine transporter -1 (GlyT-1) have strongly been involved in the glutamatergic hypothesis in SZ. New treatments based in the glutamatergic neurotransmission could improve the cognitive deficits in this disease (This figure has been modified from ref [8]).

Another point of contact between astrocytic function and glutamatergic synapse is Kynurenic acid (KYNA). It is produced by astrocytes as a metabolite of the kynurenine pathway of tryptophan degradation. It is formed by irreversible transamination of kynurenine catalyzed by enzymes kynurenine aminotransferase (KAT) I and II (see Fig. (**1**)). Endogenous levels of KYNA antagonize two different receptors, which have a critical role in cognitive processes, namely the glycineB site of the NMDAR and the alfa7 nicotinic acetylcholine receptor. Therefore, it is suggested that a compensation to NMDAR hypofunction by modulating KYNA levels may be a rational therapeutic alternative for SZ [51]. This could be achieved by the use of inhibitors of KAT II as well as by other manipulations of the kynurenine pathway metabolism [52].

In summary, astrocytic function seemingly plays a relevant role in the physiology of glutamatergic synapse, and -more importantly- in the SZ pathogenesis. There are solid experimental data to support this statement. In this context, we hypothesize that the pharmacological modulation of astrocytic functions may offer a promising target for novel and efficacious treatment of SZ cognitive alterations. This experimentally testable hypothesis may raise controversy among experts, but the current published evidence and ongoing experimental work point towards a pivotal role of astrocytic functions in SZ.

NEW METABOTROPIC GLUTAMATERGIC MODULATORS

The rational design of new organic molecules capable of modulating glutamatergic neurotransmission is a critical goal in the context of the glutamatergic hypothesis of SZ [53]. The rational synthesis of new therapeutic agents can be approached in two different ways. On one side, there is the classical design of NMDA, AMPA/kainate agonists [54, 55], which can directly regulate glutamatergic neurotransmission and potentially enhance cognitive performance. On the other side, the synthesis of mGluR ligands, more specifically, Group I mGluRs (mGluR-1 and mGluR-5, see Fig. (**1**)). These receptors are known to increase calcium release from endoplasmic reticulum, and activate transcription factors and other effector mechanisms involved in neuronal excitability and long- and short-term plasticity. More specifically, mGluR-1 selective agonists can modulate glutamatergic neurotransmission by either promoting pre-synaptic release of glutamate or by modulating post synaptic PCK-dependent pathways (Fig. (**1**)). The pre-clinical and clinical evidence on mGluRs and their role in SZ has been extensively reviewed by Gaspar et al [53]. In this work, we emphasize the role of certain chemical families as potential sources of new lead compounds with affinity for mGluRs and potential cognitive enhancing properties. A remarkable example of the potential mGLUR agonists in the treatment of SZ was recently reported by Patil et al [*56*]. In this critical trial the authors demonstrated a significant improvement of both positive and negative symptoms of SZ, and a safety profile comparable to placebo in mGLUR agonists. Several different other agonists and antagonists of the mGluRs, typically analogues of glutamate, quisqualate, or phenyl glycine, have been proven to interact with the agonist (orthosteric) binding site of mGluRs [57]. For example, Willardine and 1H-Cyclopentapyrimidine-2,4 (1H,3H)-dione-related compounds have recently emerged as promising leads for new cognitive enhancing agents [58]. Molecules from these chemical families have been reported to bind mGluR-1. According to these authors [*58*], successful synthetic approaches to new mGluR-1 ligands may result from the transformation of Willardine into halogenated more lipophilic –and probably more resistant to biotransformation- compounds. Unfortunately, the specific pharmacophore groups of Willardine derivatives interacting with mGluRs are not yet known. This makes difficult to rationally design libraries of new lead compounds. However, this same pattern of structural modification aimed to obtain halogenated -and more lipohilic- ligands is common to mGluR-5 selective modulators [59]. A number of pyrazole derivatives reported as selective allosteric modulators of mGluR-5 are highly sensitive to changes in polarity and positioning of halogen groups. More specifically, mGluR-5 modulators with polar groups in the phenyl ring display significantly less potency than their halogenated – and less polar- analogs. Interestingly, less polar molecules also penetrate blood-brain-barrier (BBB) more efficiently. As the glutamatergic hypothesis of SZ has gained considerable relevance, it is expected that more small molecules targeting cognitive decline will be designed on the base of this hypothesis. In this context, combinatorial chemistry will soon generate great libraries of new potential mGluRs agonists, with common structural features to those currently known natural and synthetic ligands. We propose, that the above mentioned structure-affinity concepts should be taken into consideration for the rational design of new cognitive enhancing agents targeting mGluRs. It is worth to mention that BBB penetration is a highly relevant aspect of the rational design of CNS-acting drugs, but is not often unaddressed in scientific contributions describing the synthesis of new mGluRs ligands.

DISCUSSION

The explanatory hypothesis of SZ as a complex process resulting from glutamatergic neurotransmission imbalances, based on NMDAR dysfunction, is supported by robust evidence. It is unlikely that this dysfunction is an isolated phenomenon, probably regulatory mechanisms influencing NMDAR function are also compromised to different extents in these patients. Along time increasingly complex proposals have been constructed to explain the clinical features and the therapeutics of the disease. The design of a definitive comprehensive model by integrating the variety of neurobiological findings is a challenging task. For example, there are several reports of schizophrenic have impaired glucose tolerance [*60*] and metabolic syndrome without use of antipsychotic treatment [*61*]. Also, it has been recently stated that drug- naive SZ patients and its relatives have elevated risk of diabetes and also low risk of obesity, suggesting a possible genetic predisposition to impaired glucose metabolism in this kind of patients *[62]*. These and other reports support the hypothesis that a failure of glucose uptake could misbalance the production of glutamate due to an inadequate glucose transport at high glucose demands leading to clinical spectrum of first onset SZ onset [*63*]. Thus, the altered regulation of glucose brain could constitute another dysfunctional

mechanism of NMDAR in these patients. Also, encompassing the glutamatergic dysfunction, but beyond it, several studies have focused on the contribution of inflammatory processes in the brain and the potential contribution of anti-inflammatory drugs to the relief SZ clinical symptoms *[64]*. Therefore, in the future the treatment of SZ and especially its CDs will target these regulatory elements. It is very likely that future efficacious treatments will address more than one molecular mechanism. In summary, the present review explores the evidence of the glutamatergic hypothesis in SZ and its importance in the CDs in this disease and new insights for the development of pharmacological approaches to SZ. These new treatments might consider the complexity of the "tripartite synapse", namely, the existence of bidirectional communication between astrocytes and neurons. The development of new molecules with more than one mechanism or interconnected mechanisms of actions will more likely produce improvement of the cognitive dysfunctions observed in SZ.

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