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The Glutamatergic Aspects of Schizophrenia Molecular Pathophysiology: Role of the Postsynaptic Density, and Implications for Treatment

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Abstract: Schizophrenia is one of the most debilitating psychiatric diseases with a lifetime prevalence of approximately 1%. Although the specific molecular underpinnings of schizophrenia are still unknown, evidence has long linked its pathophysiology to postsynaptic abnormalities.

The postsynaptic density (PSD) is among the molecular structures suggested to be potentially involved in schizophrenia. More specifically, the PSD is an electron-dense thickening of glutamatergic synapses, including ionotropic and metabotropic glutamate receptors, cytoskeletal and scaffolding proteins**,** and adhesion and signaling molecules. Being implicated in the postsynaptic signaling of multiple neurotransmitter systems, mostly dopamine and glutamate, the PSD constitutes an ideal candidate for studying dopamine-glutamate disturbances in schizophrenia. Recent evidence suggests that some PSD proteins, such as PSD-95, Shank, and Homer are implicated in severe behavioral disorders, including schizophrenia. These findings, further corroborated by genetic and animal studies of schizophrenia, offer new insights for the development of pharmacological strategies able to overcome the limitations in terms of efficacy and side effects of current schizophrenia treatment. Indeed, PSD proteins are now being considered as potential molecular targets against this devastating illness.

The current paper reviews the most recent hypotheses on the molecular mechanisms underlying schizophrenia pathophysiology. First, we review glutamatergic dysfunctions in schizophrenia and we provide an update on postsynaptic molecules involvement in schizophrenia pathophysiology by addressing both human and animal studies. Finally, the possibility that PSD proteins may represent potential targets for new molecular interventions in psychosis will be discussed.

Keywords: Dopamine, homer, kalirin, NMDA, PSD-95, psychosis, shank, synaptic plasticity.

INTRODUCTION

Schizophrenia is a devastating mental disorder characterized by multiple symptom domains, notably positive symptoms (hallucinations and delusions), negative symptoms (i.e. blunted affect, poverty of speech, curbing of interest and social withdrawal), and cognitive disturbances with a slow but progressive functional decline. Although schizophrenia has low lifetime prevalence (1%), it remains one of the most disabling mental disorders, with profound consequences on the individual's personal, social, and occupational functioning. Moreover, all currently approved antipsychotic drugs still share the targeting of dopamine D_2 receptors and are often effective for treating positive symptoms, but have been proven to slightly impact negative and cognitive symptom domains of schizophrenia [1].

Albeit considerable research efforts have been made to unveil the molecular underpinnings of the disease, major gaps and conflicting results still exist. Despite the elusiveness of the results, converging lines of evidence point to glutamatergic synaptic dysfunction and dopamine-glutamate aberrant interaction as major, albeit not unique, structural and functional players in the pathophysiology of the disease [2-7].

Indeed, treatment strategies targeting the glutamatergic system have been proposed also as add-on therapies to current antipsychotic drugs commonly impacting the dopaminergic neurotransmission [8].

Glutamatergic dysfunction has long been suggested to involve an imbalance in the amount and distribution pattern of glutamate receptors in key cerebral areas. However, the lack of consistent evidence has warranted further research to refine the role of glutamate and to take into account the abnormalities in glutamatergic post-receptor molecules implicated in neurotransmitter signaling [6]. Therefore, recent lines of research have highlighted the putative role of a range of post-receptor molecules in schizophrenia, all of which contribute to glutamatergic signaling and promote the interplay between glutamate receptors and other neuro-transmitter systems.

In particular, dysfunctions in glutamate and dopamine interactions have been regarded as possible molecular mechanisms involved in schizophrenia pathophysiology, and

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postsynaptic density (PSD) proteins have been suggested to contribute to such aberrancies.

More specifically, PSD proteins are part of a complex ultrastructure, principally located in the dendritic spines of excitatory glutamatergic post-synapses. This ultrastructure represents a paradigmatic example of a highly-organized molecular domain, whose members may play a pivotal role in neurobiology and, possibly, in the pharmacotherapy of schizophrenia. Indeed, the PSD constitutes the integration site of synaptic signaling downstream of several receptor systems, mainly the dopaminergic and glutamatergic systems. Over the past years, PSD proteins have gained considerable attention by neurobiologists in their endeavors to lay down the molecular mechanisms of schizophrenia.

Thus, the main purposes of this review are to: i) summarize and critically discuss reports on the putative role of PSD proteins in the pathophysiology of schizophrenia; ii) to depict future avenues of research in schizophrenia pharmacotherapy based on the modulation of PSD proteins by current antipsychotic agents. Furthermore, a preliminary section will briefly outline the literature starting from the early steps of the glutamatergic hypothesis of schizophrenia to the N-methyl-D-aspartate (NMDA) Receptor Hypofunction (NRH) hypothesis.

THE GLUTAMATERGIC SYSTEM

Glutamate receptors comprise ionotropic (ligand-gated cation channels) and metabotropic (G-protein coupled) receptors. Ionotropic receptors, named after the agonists that were originally characterized to selectively activate them, are subdivided into three groups: *i*) NMDA-sensitive, *ii*) α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA)-sensitive, and *iii*) 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine (Kainate)-sensitive receptors (for a review, see: [9]). Metabotropic receptors (mGluRs) have been grouped in three families (type I, type II, and type III) based on homology in their pharmacology and protein sequence.

NMDA Receptors

NMDA receptors are tetrameric structures composed of seven subunits: GluN1, GluN2A-D, GluN3A-B. GluN1 is the mandatory subunit in functional NMDA receptors. Activation of NMDA receptors requires two obligatory co-agonists, glycine and glutamate, whose binding sites are localized on the GluN1 [10] and GluN2 [11] subunits, respectively. Once activated by agonists, NMDA receptors mediate Ca^{++} and Na^{+} influx within neurons.

NMDA receptors are located within the PSD, a protein ultrastructure of the cytoskeleton. PSD proteins include scaffolding and signaling proteins that are implicated in synaptic plasticity [12, 13]. Within the PSD, downstream glutamatergic neurotransmission is finely tuned, thereby enabling cross talks with signaling pathways from other neurotransmitter systems [14].

NMDA receptors show several binding sites for agonists, antagonists, or modulator agents, thus providing a very complex overall regulation of the receptor.

NMDA is the most selective agonist of NMDA receptors and the most used ligand for the glutamate recognition site [15]. Glycine is an endogenous agonist ligand to the glycine-binding site. Another agonist is D-Serine, a potent endogenous ligand present at the same site [16]. Partial agonists at glycine binding site comprise L-alanine, D-cycloserine, and R(+)-3-amino-1-hydroxypyrrolid-2-one [(+)-HA-966] [17].

Blockers of the NMDA receptor ion channel pore include the highly potent compounds ketamine and phencyclidine (PCP) [17]. These compounds are trapped within the closed conformation of the channel pore, thus impeding Ca^{++} influx. Given their high affinity for NMDA receptors and the slow reversibility of their binding, they have been named as non-competitive antagonists of NMDA receptors and may elicit psychosis in humans and schizophrenia-like behavior abnormalities in animals [7, 18].

Non-NMDA Ionotropic Receptors

AMPA receptors are tetrameric structures formed by the assembly of four distinct subunit types, GluA1-4, which are the products of four different genes [9]. Once activated, AMPA receptors facilitate neuronal influx of Na^{+} and Ca^{++}. AMPA receptors containing GluA2 subunits are impermeable to Ca^{++}, whereas those not containing GluA2 subunits are Ca^{++}-permeable and show marked inward rectifier properties [9].

To date, pharmacological studies on agonists, partial agonists, antagonists, and non-competitive antagonists at AMPA receptors for human use have been largely inconclusive [19]. One serious limitation is the fast occurrence of homeostatic feedback regulations, e.g. desensitization and/or deactivation, upon agonist or antagonist binding. However, this limitation has been overcome by the use of positive allosteric modulators, such as aniracetam. A recent study has indeed demonstrated that these modulators, which are active in animal models of cognition, facilitate AMPA-receptor-mediated synaptic activity [20].

Other modulators include a series of benzamide derivatives, named AMPAkines. These AMPA-receptor modulators are now being tested in clinical trials for the treatment of human cognitive diseases, including cognitive failure and moderate dementia [21].

The other type of non-NMDA ionotropic receptors is the Kainate receptors, which are most presumably heteromeric tetramers belonging to two related family of subunits: GluK1-3 and GluK4,5 [22]. Kainate receptors are Na^{+} and Ca^{++} permeable ion channels. However, the study of Kainate receptor molecular pharmacology and electrophysiology has been difficult because of the lack of selective ligands. Only recently have some selective agonists and antagonists for Kainate receptors been identified, thus allowing for more detailed and promising research [22].

Metabotropic Receptors

Eight different subtypes of mGluRs have been described and subdivided into three families according to sequence homology, second messenger coupling, and pharmacology

[23]. Type I mGluRs (*i.e.* mGluR1 and mGluR5) are $G_{q/11}$-protein-coupled receptors that are preferentially expressed on the postsynaptic dendrites and somas of neurons. Activation of type I mGluRs increases NMDA receptor currents [24] and may modulate the phosphorylation state of the receptor [25]. Basically, type I mGluRs increase neuronal excitability and promote synaptic plasticity [26]. Type II mGluRs (*i.e.* mGluR2 and mGluR3) play a key role as autoreceptors in glutamate terminals and are localized on postsynaptic sites and glial cells (limited to mGluR3) [27]. Type III mGluRs (mGluR4, mGluR6, mGluR7 and mGluR8) are instead predominantly localized pre-synaptically in axon terminals and modulate neurotransmitter release [28]. Both type II and type III mGluRs, albeit with peculiar molecular and pharmacological features, are coupled to $G_{i/o}$ proteins and inhibit adenylyl cyclase, thereby reducing 3'-5'-cyclic adenosine monophosphate (cAMP) levels.

THE RISE AND (PARTIAL) FALL OF THE NRH HYPOTHESIS OF SCHIZOPHRENIA PATHO-PHYSIOLOGY

From Early Evidence to the NRH Hypothesis

One of the first evidence of an altered glutamate system in schizophrenia was provided by a report of significantly reduced glutamate levels in schizophrenia patients' cerebrospinal fluid (CSF) [29]. In the same period, the seminal discovery that PCP could act as a non-competitive blocker of the NMDA receptor ion channel prompted the hypothesis that glutamate played a role in schizophrenia [30]. In earlier years, scientists anecdotally reported that PCP exacerbated psychotic symptoms in schizophrenic abusers and generated a "schizophrenia-like" syndrome in non-schizophrenic PCP addicts [31, 32]. Psychotic symptoms in healthy subjects were almost indistinguishable from those observed in schizophrenia patients, for they mimicked the positive, negative, and cognitive symptoms of the disease [33].

Ketamine was also described to elicit psychotic symptoms. The compound was found to cause cognitive impairment in healthy individuals [34] and to exacerbate psychosis in stabilized schizophrenia patients [35, 36].

Later animal studies appeared to corroborate the hypothesis that a glutamate dysfunction could contribute to the pathophysiology of psychosis. For instance, acute PCP administration was shown to increase both locomotor activity and stereotypic motor behaviors [37], whereas subchronic PCP exposure was reported to induce behavioral sensitization [38]. Other NMDA receptor non-competitive antagonists, such as ketamine or MK-801, were also described to induce similar behavioral outcomes [39]. Moreover, these compounds were found to impair rat behaviors reminiscent of cognitive tasks in humans [40]. Notably, antipsychotic agents were found to revert behavioral alterations caused by non-competitive NMDA receptor antagonists in animals [41, 42]. Therefore, non-competitive NMDA receptor antagonists were assumed to provide a reliable and heuristic animal model of schizophrenia [43, 44]. These observations led to the hypothesis that aberrant glutamatergic transmission could potentially underlie schizophrenia pathophysiology [45].

Indeed, blockade of NMDA receptors by ketamine and PCP was seen as a molecular dysfunction mimicking memory impairment and psychosis [46]. Eventually, NRH became widely accepted as the primary lesion leading to a complex cortical-subcortical perturbation in several neurotransmitter systems [47], thereby causing psychotic symptoms.

Reports on Glutamate Receptor Anomalies in Schizophrenia

The NRH hypothesis of schizophrenia pathophysiology implied that glutamatergic alterations in schizophrenia, starting from a reduced NMDA receptor activity would perturb a number of glutamatergic and non-glutamatergic systems [47]. Accordingly, initial efforts focused on elucidating receptor anomalies that could derive from the perturbation of this putative network. However, results were not as consistent as expected.

Although numerous reports evidenced a reduction in the levels of GluN1, GluN2B, and GluN2C mRNA in multiple cortical regions of schizophrenia patients [48-53], they were subsequently challenged by several other studies that found no substantial differences with controls [54-56] (Table **1**).

More recent reports on the protein levels of NMDA receptor subunits in schizophrenia patients have also been contradictory [52, 57], although it seems that subunit density may decrease in schizophrenia patients (Table **1**).

Regarding NMDA receptors, proteomic and genetic studies on non-NMDA ionotropic receptors have recently suggested a decrease in brain tissues of schizophrenia patients [49], albeit with several conflicting data [58-61] (Table **2**).

Similarly, studies on mRNA levels of metabotropic receptors in schizophrenia patients are not consistent and appear to exclude obvious changes in gene expression [62-67]. Similar results have been described in studies evaluating the protein expression of the receptors [68-71] (Table **3**).

Obviously, significant discrepancies remain over the role of glutamate receptor abnormalities in schizophrenia patients—discrepancies most likely due to methodological issues, like limited sample selection and biochemical techniques. Thus, it could be concluded that unless new avenues of research are undertaken in this research field, these discrepancies will continue to cast a shadow over the reliability of the NRH hypothesis.

ROLE OF POST-RECEPTOR GLUTAMATERGIC MOLECULES IN SCHIZOPHRENIA

Several reports suggest that glutamatergic receptors may not be the only or the primary glutamatergic molecules affected in schizophrenia [72]. Recent studies have corroborated the view that post-receptor glutamatergic molecules, as well as perturbation of the dopamine-glutamate interplay at multiple levels, may play a pivotal role in schizophrenia pathophysiology. This evidence has

Table 1. Changes in NMDA receptor subunits in schizophrenia and psychotic patients.

NMDA Receptor Subunit	Experimental Paradigm	Experimental Finding	References
GluN1 GluN2B GluN2C	*In Situ* Hybridization	GluN1, GluN2C, and GluN2C mRNA expression is lower in the thalamus of schizophrenia patients than in healthy controls, especially in the nuclei with projections to the limbic system	Ibrahim *et al*., 2000 [49]
	Receptor Autoradiography	[3H]ifendopril and [3H]MDL105,509 binding to polyamine and glycine site, respectively, of NMDA receptors is reduced in the thalamus of schizophrenia patients as compared to healthy controls	
GluN1 exon 5, 21 and 22-containing isoforms	*In Situ* Hybridization	Reduction in GluN1 transcript in the thalamus of schizophrenia patients is restricted to GluN1 exon 22-containing isoform, and is correlated to the increase in PSD-95, NF-L, and SAP102 postsynaptic protein expression	Clinton *et al*., 2003 [50]
GluN1 GluN2A-D GluN3A	*In Situ* Hybridization	Significant decreases in perirhinal cortical expression of GluN1 in bipolar depressed patients, GluN2A in major depressed patients, and GluN2B in both bipolar and major depressed patients	Beneyto *et al*., 2007 [51]
	Receptor Autoradiography	Significant reduction in hippocampal [3H]MK-801 binding (intrachannel site) in schizophrenia and bipolar disorder; increases in [3H]MDL105,519 binding (glycine site) in bipolar disorder. Increased hippocampal [3H]CGP39653 binding (glutamate site) in major depression.	
GluN1 GluN2A-D	*In Situ* Hybridization	Significant decreases in GluN1 expression in PFC in schizophrenia; decreases in GluN2A expression in PFC in schizophrenia and major depression; decreases in GluN2B expression in schizophrenia.	Beneyto *et al*., 2008 [52]
	Receptor Autoradiography	No alterations in NMDA receptor binding in all the PFC.	
GluN1 isoforms (eight isoforms)	Quantitative Real Time PCR Western Blotting	No significant differences in panGluN1 subunit between schizophrenia patients and controls; however panGluN1 expression in left/right hippocampal hemispheres is significantly greater in schizophrenics than in controls. Female schizophrenics express higher panGluN1 protein in left hippocampi than controls; male schizophrenia patients express lower panGluN1 protein in left hippocampi than in controls. Significant decreases in left hippocampi of GluN1 isoform and in right hippocampi of GluN1-2b isoform in schizophrenia patients compared to controls	Vrajovà *et al*., 2010 [53]
GluN1 GluN2A-D	Quantitative RT-PCR Western Blotting SNP polymorphisms analysis SNP polymorphisms analysis	Reduction in GluN1 and GluN2C mRNA in dorsolateral prefrontal cortex of schizophrenia post-mortem brain tissues. GluN*2B* gene SNP rs180550 is correlated with reasoning deficits in schizophrenia patients and may predict GluN1 reduction in PFC	Weickert *et al*., 2012 [48]
GluN2A-D	*In Situ* Hybridization	Increased expression of GluN2B in thalamus of schizophrenia patients	Clinton *et al*., 2004 [55]
GluN2A-D	*In Situ* Hybridization	Increased expression of GluN2B in the dorsolateral thalamus of schizophrenia patients	Clinton *et al*., 2006 [56]
GluN1 GluN2A-D	*In Situ* Hybridization	Reduced expression of GluN1 and GluN2A in hippocampus.	McCullumsmith *et al*., 2007 [54]
	Receptor Autoradiography	No alteration NMDA receptor binding in all hippocampus	
GluN1 GluN3	PCR Immunoblotting	Unchanged levels of GluN1 and GluN3A in developing PFC of schizophrenia patients	Henson *et al*., 2008 [57]

Here we summarize the most relevant findings on the modifications of NMDA receptor subunit expression in relevant cerebral areas of schizophrenia and psychotic patients, along with the experimental techniques used to carry out the observations (PFC, prefrontal cortex).

Table 2. Changes in non-NMDA receptor subunits in schizophrenia and psychotic patients.

AMPA/Kainate Receptor Subunit	Experimental Paradigm	Experimental Finding	References
GluA1 GluA2 GluA3 GluK1 GluK2	*In Situ* Hybridization	Significantly lower levels of GluA1 mRNA in dorsal medial and central medial thalamic nuclei of schizophrenia patients. Significantly lower levels of GluA3 in central medial thalamic nuclei of schizophrenia patients. Significantly lower GluK2 levels in anterior, dorsal medial, lateral dorsal, central medial and ventral thalamic nuclei of schizophrenia patients.	Ibrahim *et al*., 2000 [49]
	Receptor Autoradiography	No alterations in AMPA binding sites No alterations in kainate binding sites.	
GluA1	Quantitative PCR	Increases in GluA1 mRNA levels in layer II/III and layer V of schizophrenia patients' DLPFC.	O'Connor *et al*., 2007 [60]
GluA1 GluA2 GluA3	Quantitative PCR	No alterations in thalamus of schizophrenia patients	Dracheva *et al*., 2008 [59]
GluA1 GluA2 GluA3	Quantitative PCR	No alterations in PFC of schizophrenia patients	Lyddon *et al*., 2012 [58]
GluA1 GluA2 GluA3 GluA4	Western blot Electron microscopy	No changes in the expression of the AMPA receptor subunits in the endoplamatic reticulum from schizophrenia patients DLPFC.	Hammond *et al*., 2012 [198]
GluA2 GluA4	Western blot	GluA4 significantly increased in schizophrenia DLPFC. Endo H-mediated deglycosylation of GluA2 resulted in a smaller pool of GluA2 protein in the schizophrenia sample.	Tucholski *et al*., 2013 [199]

This table reports the modifications of non-NMDA (i.e. AMPA and kainate) receptor expression in relevant cerebral areas of schizophrenia patients, along with the experimental technique used to carry out the observations (DLPFC, dorsolateral prefrontal cortex; PFC, prefrontal cortex).

prompted the investigation of the involvement of post-receptor molecules—including those belonging to the PSD—in the transduction of glutamatergic signaling and in the cross-talk between other neurotransmitter systems.

The PSD has been defined as an electron-dense thickening at the dendritic spines of glutamatergic post-synapses, a site where glutamate receptors and their signaling downstream effectors are highly concentrated [14]. The PSD comprises up to one thousand proteins, including scaffolding proteins, receptors, membrane channels, membrane trafficking proteins, GTPases, regulator proteins, kinases, phosphatases**,** and cytoskeleton proteins [14]. Whereas NMDA receptors are located within the PSD core, non-NMDA ionotropic and metabotropic glutamate receptors are located at the edge of this ultrastructure [14]. Multiple postsynaptic signaling pathways within the PSD are involved both in the transduction of glutamatergic and other postsynaptic receptor signals and in the interaction of the glutamatergic signaling pathway along with other transduction systems [73].

Revealing evidence suggests that defects in PSD proteins may be implicated not only in schizophrenia but also in developmental disorders that present similarities with some schizophrenia symptom domains like autism. Some of these shared clinical manifestations include prominent impairments in cognitive functions, such as mental retardation and negative-like symptoms (Fig. **1**). Thus, the disruption of post-receptor clusters and the loss of functional membrane glutamate receptors due to PSD dysfunction may cause complex behavioral deficits (e.g. motor, cognitive deficits).

This framework may be common to other glutamate post-receptor molecules that also seem to be implicated in the pathophysiology of schizophrenia. For instance, it has been proposed that scaffolding PSD proteins may subserve synaptic plasticity by regulating trafficking and localization of glutamatergic and non-glutamatergic receptors within the PSD [12]. Disruption of these scaffolds may cause synaptic plasticity dysfunctions leading to schizophrenia-related symptoms.

PSD-95

Expression of PSD-95 mRNA is altered differentially in several brain areas of postmortem tissues from elderly patients with schizophrenia compared to controls. Specifically, PSD-95 mRNA decreases in Broadmann area 9 of the frontal cortex [74], and increases in the orbital cortex [75] and in the thalamus [50]. However, in a younger cohort of schizophrenia patients, PSD-95 mRNA levels in the thalamus have been observed to decrease rather than increase

Table 3. Changes in metabotropic glutamate receptors in schizophrenia patients.

mGluR Receptor	Experimental Paradigm	Experimental Finding	References
mGluR3 mGluR5	*In Situ* Hybridization	No differences in mGluRs expression in PFC of schizophrenia patients and controls, except for an increase in mGluR5 expression in area 11	Ohnuma *et al*., 1998 [64]
mGluR1 mGluR2 mGluR3 mGluR4 mGluR5 mGluR6 mGluR7 mGluR8	*In Situ* Hybridization	No differences in mGluRs expression in the six thalamic nuclei of schizophrenia patients and controls	Richardson-Burns *et al*., 2000 [65]
mGluR2 mGluR3	*In Situ* Hybridization	Significant decreases in mGluR2 expression in granule cells of cerebellum in schizophrenia patients	Bullock *et al*., 2008 [66]
mGluR2 mGluR3	*In Situ* Hybridization	Significant higher levels in mGluR2 mRNA in PFC white matter of schizophrenia patients	Ghose *et al*., 2008 [67]
mGluR2 mGluR3	Western Blotting	Decreased mGluR3 protein levels in DLPFC of schizophrenia patients, with mGluR2 levels unchanged	Ghose *et al*., 2009 [70]
mGluR2	Immunohistochemistry	mGluR2 and 5HT2A receptors form functional complexes in the cortex. In post-mortem human brain from untreated schizophrenia subjects, the 5HT2A receptor is upregulated and the mGluR2 is downregulated, a pattern that could predispose to psychosis.	Gonzalez-Maeso *et al*., 2008 [63]
mGluR2 mGluR3	Western Blotting Immunocytochemistry	Comparable levels of mGluR expression in Broadman area 46 of the DLPFC in schizophrenia patients and in controls	Crook *et al*., 2002 [68]
mGluR1 mGluR2 mGluR3 mGluR4 mGluR5 mGluR6 mGluR7 mGlur8 mGluR8	Western Blotting	Increases in mGluR1a and mGluR2/3 immunoreactivity in the PFC in schizophrenia. No changes in mGluR4a or mGluR5 expression. No changes in overall mGluR expression in the striatum	Gupta *et al*., 2005 [69]
mGluR3	Western Blotting	Significant decreases in the dimeric/oligomeric forms of mGluR3 in schizophrenia patients compared with control subjects, but no significant changes in total mGluR3 levels	Corti *et al*., 2007 [71]

This table summarizes the reports on the changes in metabotropic glutamate receptor expression in schizophrenia patients (DLPFC, dorsolateral prefrontal cortex; PFC, prefrontal cortex).

[55]. The discrepant levels of PSD-95 gene expression may thus reflect age-related changes or the severity of the illness of younger patients compared to the elderly ones.

Studies using postmortem tissue may suffer from the limitation that gene expression and/or protein density could be altered by chronic antipsychotic treatment. However, an early study reported that PSD-95 expression was similar in schizophrenia patients under–antipsychotics within 6 weeks from their death and in those who received no medications for more than 6 weeks [75].

In light of these observations, PSD-95 has been considered a putative candidate gene for schizophrenia. Conflicting results have nonetheless emerged. For example, a later study conducted in Chinese schizophrenia patients found no association between *DLG4* (the gene coding PSD-95) and schizophrenia [76]. Instead, a more recent study done in a Taiwanese sample of schizophrenia patients found an association between a functional polymorphism at the 3' untranslated region (UTR) of the *DLG4* gene with a genetic susceptibility to schizophrenia [77].

Alterations in PSD-95 mRNA expression have also been evidenced in preclinical studies investigating gene expression changes after antipsychotic administration. Although only minor changes have been detected for PSD-95 after acute antipsychotic administration [78, 79], chronic haloperidol and ziprasidone, but not sertindole, have been

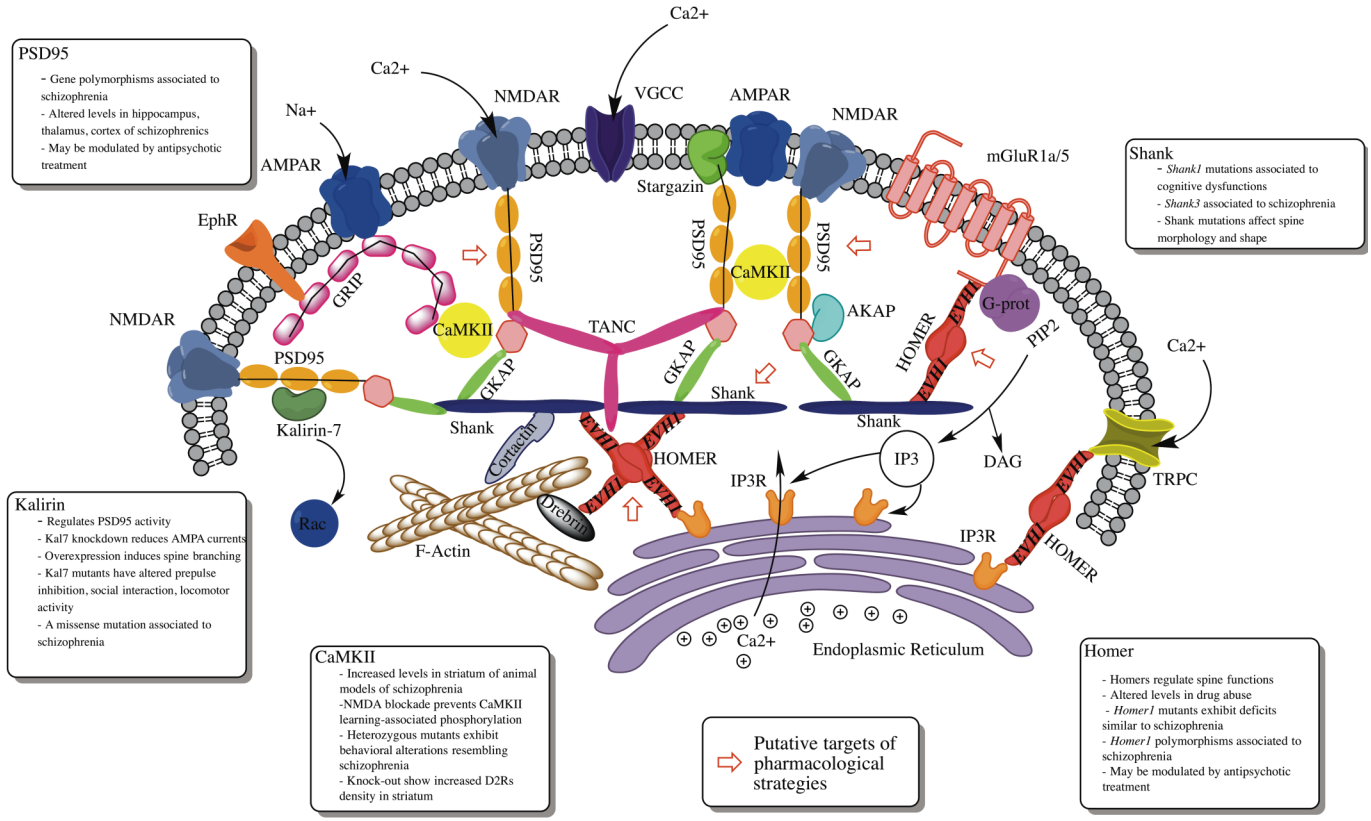

Fig. (1). Schematic Representation of the Postsynaptic Density. In this picture, we provide a simplified representation of a postsynaptic density (PSD) ultrastructure. For the sake of clarity, ultracellular organelles as well as less relevant proteins are not depicted. The call-outs describe the pathophysiological role of the proteins discussed in the text. NMDAR: N-methyl-D-Aspartate Receptor. EphR: Ephrin Receptor. AMPAR: Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid Receptor. VGCC: Voltage-Gated Calcium Channel. mGluR1a/5: type 1a/5 metabotropic glutamate receptor. TRPC: Transient Receptor Potential Cation channels. GRIP: Glutamate Receptor Interacting Protein. CaMKII: Calcium/Calmodulin-Dependent Kinase II. Rac: Ras-related C3 botulinum toxin substrate. GKAP: Guanylate Kinase-Associated Protein. EVH1: Ena/VASP Homology 1 domain. TANC: TRP- ankyrin repeat- and coiled-coil region containing protein. AKAP: A-Kinase Anchor Protein. PIP2: phosphatidylinositol biphosphate. IP3: inositol triphosphate. IP3R: IP3 Receptor. DAG: Diacylglycerol.

shown to significantly increase gene expression in both the rat cortex and the striatum [80, 81]. These observations suggest that sustained and potent blockade of dopaminergic receptors may trigger plastic adaptations at glutamatergic synapses, thereby representing one of the molecular mechanisms of antipsychotic action.

Some studies suggest that PSD-95 also facilitates the activation of erbB4, a protein that acts as a receptor for neuregulin1 (NRG1). Interestingly, NRG1 has been proposed as a candidate gene for schizophrenia and has been implicated it in the modulation of NMDA receptor signaling [82]. Consistently, another study has revealed that although NRG1-induced activation of erbB4 markedly increases in the prefrontal cortex of schizophrenia patients, levels of NRG1 and erbB4 are unchanged in both patients and controls [83]. In the same sample, both an increased association between PSD-95 and erbB84 and a pronounced NRG1-mediated suppression of NMDA receptor activation have been observed in patients compared to controls [83]. These observations suggest that PSD-95 may cooperate with NRG1 by interacting with erbB84, thereby affecting NMDA-mediated glutamatergic transmission in schizophrenia. Consistently, perinatal exposure to PCP triggers long-term changes of erbB4, NRG1, NMDA receptor subunits, and PSD-95 [84].

Overall, PSD-95 dysfunctions may predispose neurons to synaptic plasticity defects and abnormal glutamatergic signaling. A recent study reports that, when fibroblasts from schizophrenia patients are reprogrammed into human pluripotent stem cells and subsequently differentiated into neurons, their neuronal connectivity, neurite number, PSD-95 protein levels, and glutamate receptor expression are decreased [85]. These findings do indeed confirm the theory that diminished PSD-95 levels could disrupt PSD scaffolding and affect post-receptor synaptic signaling, thus contributing to the glutamatergic hypofunction hypothesized in schizophrenia.

Taken together, PSD-95 may be one of the most interesting and perhaps crucial members of the PSD network involved in schizophrenia. Future studies are indeed delving deeper into its putative role in an attempt to provide more promising insights into the intricate molecular mechanisms of schizophrenia.

Shank

In the PSD, the scaffolding protein Shank exists in three isoforms (Shank1, 2, and 3). Shank proteins bridge glutamate receptors with other scaffolding proteins, cytoskeleton factors, and intracellular effectors. Converging reports are highlighting a major role for Shank protein alterations in conditions with a strong genetic component and cognitive impairment, including schizophrenia and schizophrenia-related disorders.

Knock-out mice for *Shank1* gene exhibit impaired memory functions, weaker basal synaptic transmission, reduced number of dendritic spines, and diminished PSD density compared to wild-types [86]. Moreover, *Shank1* knock-out mice perform worse than their wild-type littermates in social communication tasks, regarded as animal behavioral correlates of the social and communicative impairments commonly associated with schizophrenia [87]. Consistently, a mutation in the *Shank1* gene promoter region has been associated with working memory deficits in patients with schizophrenia and in subjects at risk for psychosis [88].

Disruption of the *Shank3* isoform has been implicated in a rare genetic disease such as the 22q13.3 deletion syndrome, a condition characterized by speech alterations, autistic behavior, and minor dysmorphic facial features [89]. Notably, a recent study has observed that regional copy number variations (CNVs) at 22q13.31 may influence the risk of schizophrenia [90]. Two *de novo* mutations have also been identified in the coding region of the *Shank3* gene in a sample of schizophrenia patients. The R1117X missense mutation results in a truncated form of the Shank3 protein, lacking the Homer-binding site [91]—a defect that causes a dramatic loss of function in a number of *in vitro* and *in vivo* assays. According to this finding, Shank interaction with Homer may have great biological relevance, since Homer-Shank complexes bridge type I mGluRs to NMDA receptors [92] and regulate the functional architecture of Ca^{++} homeostasis within dendritic spines [93, 94]. Consistently, the disruption of Homer-Shank complexes has been described to inhibit NMDA currents by type I mGluRs agonists [95]. Therefore, disruption of Homer-Shank interaction may result in impaired postsynaptic glutamatergic signaling and altered synaptic plasticity processes that may be relevant to schizophrenia pathophysiology.

Overall, Shank proteins contribute to normal dendritic spine maturation, morphology, and function. Loss of functional Shank proteins may therefore severely impair dendritic spine functions and affect synaptic plasticity, phenomena that are putatively implicated in cognitive impairment and schizophrenia-like behavioral manifestations [96]. In agreement with this view, knock-out mice for *shank3* gene exhibit self-injurious behavior, increased anxiety-like conducts, and impaired social interactions reminiscent of some schizophrenia symptom domains [97]. These mice also show an altered molecular composition of the PSD in the striatum, defects in morphology of striatal medium-sized spiny neurons' (MSN) dendritic spines, and decreased postsynaptic spikes and currents [97]. Conversely, induction of *Shank* expression in mutant mice induces spine formation in aspiny neurons and contributes to maturation and enlargement of dendritic spines [98].

These observations suggest that Shank is a key molecule in PSD organization, mainly through its interaction with Homer, which is implicated in dendritic spine morphology and function. Shank malfunctioning at the PSD may therefore underlie some synaptic pathologies leading to psychiatric disorders, like schizophrenia, by causing a loss of dendritic spine generation, aberrant post-receptor signaling, and overall reduced glutamatergic signal transduction.

Homer

Homer proteins, another family of scaffold proteins at the PSD, anchor type I mGluRs to NMDA receptors and bridge mGluRs to their intracellular downstream effectors [99]. Within the PSD, Homer proteins participate in a variety of biological functions, including glutamatergic signaling, regulation of intracellular Ca^{++} signals, cross-talk between different neurotransmitter signaling pathways, and dendritic spine plasticity [100-102]. Homer isoforms are subdivided into constitutive "long" and inducible isoforms. Long Homer isoforms (i.e. Homer1b/c, Homer2, Homer3) comprise an N-terminal Ena/VASP (EVH) domain that allows binding to other PSD proteins, and a C-terminal coiled-coil domain that enables self assembly [101]. Unlike long Homer isoforms, the inducible isoforms (i.e. Homer1a, ania-3) lack the oligomerization domain and disrupt long Homer-mediated clusters with their PSD targets.

Several genetic studies have observed a possible involvement of Homer genes in the pathophysiology of schizophrenia. In preclinical settings, expression of the *Homer1a* gene has been found significantly increased in the striatum in a condition modeling NRH, *i.e.* acute administration of neurotoxic and non-neurotoxic subanesthetic doses of ketamine [103]. Human studies found a polymorphism in the *Homer1* gene sequence significantly more expressed in schizophrenia patients than in non-affected individuals. This finding was not replicated in a second sample and only a borderline significance remained when the two samples were merged [104]. Consistently, a polymorphism in the 5' flanking region of the *Homer1* gene has also been associated with psychotic symptoms in Parkinson's disease patients [105]. Furthermore, a number of single nucleotide polymorphisms (SNPs) within the *Homer1* gene sequence have been associated with scores on the Positive and Negative Syndrome Scale (PANSS) subscales, including total, negative, and positive subscales [106]. These SNPs have also been associated with improvements in PANSS subscales after antipsychotic treatment [106]. In agreement with these human genetic studies, other reports have shown that *Homer1a* expression is consistently altered by antipsychotic treatments [79-81, 107], suggesting that the modulation of the different *Homer* transcripts may be relevant to schizophrenia therapy.

The relative ratio between long vs. inducible Homer isoforms has been considered crucial to the understanding of the numerous biological effects on the PSD microdomains—effects which may underlie synaptic plasticity dysfunctions and glutamatergic signaling alterations putatively implicated in schizophrenia. Indeed, selective induction of Homer1a is

regarded as a mechanism that rapidly and transiently changes intracellular responses to receptor activation mediated by long Homer isoforms. Notably, the Homer1a/long Homers balance has a direct impact on spine morphology and function. For instance, recruitment of long Homer *via* Shank regulates dendritic spine morphology and synaptic function [108]. On the other hand, Homer1a expression in cultured hippocampal neurons reduces spine size, PSD-95-mediated clusters, and AMPA and NMDA receptor currents [109]. Similarly, a more recent study has revealed that induction of Homer1a disrupts the long Homer-mediated link between NMDA and type I mGluRs, thus inhibiting NMDA receptor currents by type I mGluR agonist [95].

Genetic modifications of the relative long/inducible Homers ratio have also produced substantial neurochemical and behavioral outcomes that have been relevant not only to mimic some schizophrenia symptom domains but also to gain better insights into schizophrenia pathophysiology. Overexpression of the *Homer1a* transcript has been shown to impair working memory in mice [110] and to suppress mGluR5-mediated long-term depression [111]. However, although knock-out of the *Homer1* gene causes the simultaneous loss of both long and inducible Homer1 isoforms, it virtually mimics the loss of long Homer mediated clusters as in the case of Homer1a induction. Accordingly, *Homer1* knock-out has been described to impair Long Term Potentiation (LTP) and spatial learning. This loss can be recovered by hippocampal injection of the Homer1c gene *via* a recombinant adeno-associated virus (AAV) vector [112].

Genetic studies, in addition to having revealed *Homer1* involvement in LTP and spatial learning, have also highlighted its relevance in several behavioral tasks found disrupted in schizophrenia preclinical models. One study, for instance, has reported that *Homer1* knock-out mice exhibit disrupted prepulse inhibition, impaired working memory performance, and increased locomotor response to MK-801 and amphetamine [113]. These findings have also been confirmed by one later study that subjected male *Homer1* knock-out mice to a battery of tests to evaluate sensory, motor, social, emotional and learning/memory functions. In this study homozygous mice exhibited poor motor coordination and learning deficits, whereas heterozygous mice manifested increased aggressive behaviors in social interactions [114]. In another study, overexpression of the *Homer1c,* but not of the *Homer1a* transcript, in the prefrontal cortex of *Homer1* knock-out mice reverted the cognitive and sensorimotor impairment and augmented sensitivity to cocaine consequent to *Homer1* gene deletion [115]. In the same paradigm, *Homer1a* overexpression partially reversed impairment in behavioral adaptation to repeated stress observed in knock-out mice [115].

These results suggest that the different *Homer1* transcripts may control different behavioral manifestations. Specifically, the Homer1a isoform appears to be prominently implicated in cognitive and locomotor behaviors. Accordingly, transgenic mice overexpressing *Homer1a* in striatal MSNs exhibit reduced spontaneous locomotor activity, defective motor coordination, and defective motor learning compared with wild-type littermates [116]. Moreover, they show more pronounced amphetamine-induced locomotor hyperactivity and stereotypy [116]. In addition, heterozygous tottering mice, but not homozygous tottering mice—an animal model of spontaneously occurring motor disturbances reminiscent of antipsychotic-induced motor side-effects—express higher levels of *Homer1a* in striatum compared with wild-type mice [117]. Therefore, evidence that Homer1a induction is associated with motor impairments could suggest a role of this isoform also in antipsychotic-induced motor side effects.

Altogether these results suggest that the balance between Homer1a and long Homers within the PSD may provide a complex and finely tuned regulation of postsynaptic functions. Indeed, converging evidence has underscored that disruption of this balance may elicit those dendritic spine pathologies that putatively underlie the behavioral patterns of schizophrenia-spectrum disorders.

CaMKII

Ca^{++}/Calmodulin Kinase type II (CaMKII) is a Ser/Thr kinase that is prominently activated by Ca^{++} entry through NMDA receptors. CaMKII modulates several steps of the glutamatergic signaling pathway and the glutamatergic cross-talk with other neurotransmitter systems.

Although evidence on the role of CaMKII in neurological and psychiatric disorders is still inconclusive, several studies point to CaMKII as one of the potential molecular mechanisms implicated in schizophrenia pathophysiology. One study indicates that gene expression of the α*CaMKII* subunit increased in the striatal subregions in an animal model of schizophrenia generated by acute ketamine administration [103]. However, no change has been described in rat cortical regions after PCP administration [118]. Moreover, CaMKII protein levels decrease in rat prefrontal cortex after chronic PCP [119]. Interestingly, chronic PCP exposure in mice impairs latent learning and prevents learning-associated phosphorylation of CaMKII, eliciting reduced CaMKII activity [120].

Heterozygous mice for a null mutation in the α*CaMKII* gene exhibit impaired neuronal development in the dentate gyrus and a number of behavioral abnormalities putatively relevant to schizophrenia, among which working memory deficits [121]. Moreover, *αCaMKII* knock-out mice show increased striatal density of dopamine D_2 receptors in their high affinity status, a feature that may explain the behavioral alterations reminiscent of schizophrenia in this model [122]. CaMKII activity is also impaired in knock-out mice for *LRRC7*, the gene coding for the abundant PSD scaffold protein densin-180. This animal model exhibits several behavioral abnormalities considered endophenotypes of schizophrenia [123].

Evidence for CaMKII association with schizophrenia in human studies is limited. *α*CaMKII levels in the prefrontal cortex have been found unaffected in a small sample of schizophrenia patients compared with healthy controls [124]. However, increased mRNA levels of β*CaMKII* have been described in postmortem frontal cortex tissues from schizophrenia patients [125].

Kalirin

Kalirin is a family of proteins that is highly enriched in the central nervous system (CNS) and virtually absent elsewhere. The most abundant member of this family protein is kalirin-7, which is prominently localized in the PSD of excitatory dendritic spines on cortical pyramidal neurons [126]. Kalirin**,** a guanine nucleotide exchange factor (GEF), is activated by the EphB receptor-mediated signaling pathway [127]. Its function is to promote the activity of small GTPases, including Rac1, RhoA, and RhoG, which are in turn implicated in actin cytoskeleton remodeling, spine morphology, and synaptic plasticity [128].

Because of its main distribution within PSD, Kalirin-7 is regarded as a regulator of signal transduction pathways, which may enable membrane proteins to connect to the actin cytoskeleton. Through its interaction with PDZ proteins, such as PSD-95, Kalirin-7 is targeted to the PSD where it regulates dendrites morphogenesis [129]. Indeed, it has been demonstrated that expression of a mutant isoform of Kalirin-7, which lacks the property to bind to PSD-95, precludes its translocation to the PSD and is associated with a reduced number of spines in cultured hippocampal neurons [129].

Moreover, Kalirin-7 interacts with several other targets within the PSD and controls a number of postsynaptic functions, including receptor trafficking and vesicle secretion. In cultured neurons, knockdown of Kalirin-7 expression reduces the spine content of GluA1 subunits and diminishes the frequency and the amplitude of AMPA receptor-mediated postsynaptic potentials [130]. Kalirin-7 is also thought to regulate the activity-dependent structural remodeling and functional plastic changes within dendritic spines. Activation of NMDA receptors activates Kalirin-7 *via* phosphorylation by CaMKII [130]. In turn, Kalirin-7 activates small GTPases and favors the rapid activity-dependent enlargement of dendritic spines, which is considered one of the mechanisms of synaptic plasticity [130]. Consistently, studies show that overexpression of Kalirin-7 increases dendrite branching and induces spine formation in aspiny cultured hippocampal neurons [131] through recruitment of PSD-95, GluN1 and GluA1 subunits. Indeed, transgenic mice lacking the terminal exon unique to Kalirin-7 exhibit decreased cortical and hippocampal spine density and reduced AMPA receptor-mediated synaptic transmission [132, 133]. Knock-out mice for Kalirin-7 have also decreased levels of GluN2B subunit surface expression and of NMDA receptor currents in cortical pyramidal neurons [134].

Concerning the functional significance of Kalirin-7 on behavioral and cognitive responses, studies have indeed shown that in *Kalirin-7* transgenic mice, behavioral phenotypes, such as working memory and learning in passive avoidance tasks, are impaired. However, in the same animal model, other behavioral tasks, including object recognition, radial arm maze, and reference memory, are not impaired [132, 133]. *Kalirin-7* transgenic mice also exhibit reduced prepulse inhibition, diminished social interactions, and increased locomotor activity when compared with wild-type littermates [132]. These phenotypes suggest that the *Kalirin-7* knock-out mice may represent an animal model relevant to schizophrenia.

Kalirin-7 has been implicated in the mechanisms leading to alteration in dendritic spines consequent to impaired glutamatergic neurotransmission. Indeed, duration and intensity of Rac1 activation in response to NMDA receptor stimulation has been attributed to DISC1-mediated anchoring of Kalirin-7 and consequent restriction of Kalirin-7 access to Rac1, which in turn reduces Rac1 function [135].

Suggestive evidence indicates that mutations or alterations in Kalirin represent a genetic risk factor for schizophrenia. One of these studies found a genetic association between multiple rare (<1%) missense mutations in *Kalirin* gene and schizophrenia in a Japanese population [136].

Another study evidenced, instead, that an imbalance between different *Kalirin* gene isoforms might also be involved in schizophrenia. For example, while loss of *Kalirin-7* may be associated with some aspects of schizophrenia, Kalirin-9 overexpression has been detected in postmortem auditory cortex of schizophrenia patients [137]. Thus according to this finding, sustained but not short-term Kalirin-9 overexpression in cultured primary neurons seems to account for the reduction in dendritic length and complexity [137].

PDZ Proteins

SAP-97 is an AMPA receptor binding PSD protein whose gene expression has been found increased in adult rats exposed to acute PCP [138]. According to preclinical data, SAP-97 protein amount has been found decreased in the prefrontal cortex of chronic schizophrenia patients [139]. Intriguingly, this finding has been associated with reduction of GluR1 amount in the same brain region [139]. Putative confounding action of neuroleptic treatment has been ruled out with the finding that rats treated subchronically with antipsychotics did not show changes in frontal cortex SAP-97 protein amount [139]. However, in a more recent study, SAP-97 protein amount has been found increased, rather than decreased, in the prefrontal cortex of schizophrenia patients [140]. Divergence in sample collection or in experimental techniques may explain inconsistency in results.

Single nucleotide polymorphisms in *SAP-97* gene have been tentatively associated to schizophrenia, although the association appears to have limited statistical significance [141] and may be restricted to male subjects [142]. Nonetheless, SAP-97 appears an intriguing candidate for further investigation.

Significant changes of protein amount in postmortem tissue from schizophrenia patients have also been reported for other PSD members, including: PSD93; NF-L; SAP-102 [50, 54, 143-145]. However, the functional significance of these changes for schizophrenia susceptibility is yet to be elucidated.

The protein interacting with C-kinase-1 (PICK1) is a scaffolding protein implicated in the targeting and clustering of neuronal receptors and amine transporters, which interacts

with serine racemase [146]. PICK1 coding gene is located in a putative chromosomal locus of susceptibility for schizophrenia and a polymorphism within this gene has been positively associated with schizophrenia in both a Taiwanese [147] and a Japanese population [146]. It has been suggested that this PICK1 allelic variant might impair glutamate receptor surface expression and/or synaptic trafficking and could increase susceptibility for schizophrenia [148]. However, in a larger Japanese sample, no association was found between PICK1 gene polymorphisms and schizophrenia [149].

Densin-180 is a PSD protein forming a complex with CaMKII and actin cytoskeleton. Knock-out mice for *LRRC7*, the gene coding densin-180, have been described to display abnormal behaviors recalling some symptoms of schizophrenia and of autism-spectrum disorder [123]. Loss of densin-180 in these mutant mice has been associated with changes of spine morphology, reduced localization of mGluR5 in the PSD, impairment of mGluR- and NMDA receptor-dependent long-term depression, alterations of NMDA receptor regulation of CaMKII activity [123].

Although data on PSD members in schizophrenia are still elusive, the current body of evidence let hypothesize that disruption of PSD organization or architecture may perturb glutamatergic signaling and may contribute to the pathophysiology of behavioral abnormalities.

POSTSYNAPTIC MECHANISMS OF DOPAMINE-GLUTAMATE INTERPLAY: RELEVANCE FOR SCHIZOPHRENIA

Based on the observations that both glutamatergic and dopaminergic dysfunctions have been demonstrated in schizophrenia patients and in preclinical models of schizophrenia, the imbalance between dopamine and glutamate transmission has received increasing attention as one of the main mechanisms involved in schizophrenia pathophysiology [150, 151].

Recent findings have demonstrated that PSD proteins contribute to the interaction between dopamine and glutamate systems at receptor and post-receptor levels. Therefore, PSD protein alterations may in turn cause dysfunctions of dopamine-glutamate interplay.

It has been suggested that dopamine D_1 and NMDA receptors may trans-activate reciprocally. Activation of D_1 receptors triggers the rapid trafficking of NMDA receptor subunits, causing increased GluN1 and GluN2B subunit amount in dendritic spines, increased surface expression, and increased clustering with postsynaptic scaffolding molecules, such as PSD-95 [152]. D1 receptor-mediated enhanced trafficking of NMDA receptors is regulated by Fyn kinases [106], but other intracellular pathways may also be involved, including PKA, PKC, or ERK [153]. On the other hand, it has been reported that activation of NMDA receptors favors recruitment of D_1 receptors to the plasma membrane of cultured rat neostriatal neurons [154].

Moreover, a physical interaction leading to the formation of an NMDA/D_1 receptor hetero-oligomer has been reported [155]. In particular, D_1 receptors couple to GluN1 subunits of NMDA receptors. The interaction between D_1 receptors and GluN1 subunits promotes NMDA-mediated increases of plasma membrane insertion of D_1 receptors [156]. Moreover, in cultured hippocampal neurons, activation of NMDA receptors enhances D_1 receptor-mediated cAMP accumulation [156]. Finally, activation of D_1 receptors in hippocampal neurons enables CaMKII association to GluN1 subunits and promotes CaMKII activity, thereby up-regulating NMDA receptor-mediated CaMKII-dependent induction of LTP [157].

A recent study demonstrated that PSD-95 may function as a brake of this D_1/NMDA receptor interaction, presumably to prevent excessive dopamine/glutamate stimulation of postsynaptic neurons and excitotoxicity. PSD-95 has been shown to abolish NMDA receptor-dependent inhibition of D_1 receptor internalization, thus disrupting association between GluN1 subunit and D_1 receptors and impeding NMDA receptor-dependent enhancement of D_1 receptor signaling [158]. In cultured cells, co-expression of PSD-95 and D_1 receptors inhibits the D_1-mediated cAMP accumulation [159]. This phenomenon could be due to both a PSD-95-mediated increased D_1 receptor endocytosis and a reduced D_1 expression at the cell surface [159]. Consistent with this finding, mutant mice lacking PSD-95 exhibit heightened behavioral responses to D_1 receptor agonists or amphetamine [159].

Imbalance of the dopamine-glutamate interplay may trigger adaptive changes involving PSD proteins. Long-term nigrostriatal dopamine depletion in rat, a model of Parkinson's disease, has been demonstrated to increase phosphorylation status and activity of CaMKII [160] and subsequently CaMKII-mediated phosphorylation of AMPA receptor GluA1 subunit, albeit only after sustained dopamine depletion. Therefore, persistent hypodopaminergia may lead to postsynaptic changes involving glutamate neurotransmission aimed at restoring normal postsynaptic neuron excitability. Consistent with this view, activation of D_2-like dopamine D_4 receptors, which are known to exert inhibitory action on postsynaptic excitability, has been shown to induce rapid translocation of activated CaMKII from cytosol to postsynaptic sites in cultured prefrontal cortex (PFC) neurons [56]. In the same paradigm, increases in CaMKII-dependent phosphorylation of AMPA receptor GluA1 subunits and in the amplitude of AMPA receptor currents have also been observed [161].

Evidence shows that NMDA-mediated excitatory postsynaptic currents are dose-dependently modulated by dopamine in isolated PFC pyramidal neurons [162]. In particular, low to intermediate doses of dopamine increase NMDA currents, presumably *via* a prominent action at D_1 receptors. By contrast, high dopamine doses have been found to reduce NMDA currents and to activate both D_1 and D_2 receptors with a dominant effect of D_2 vs. D_1 receptors [162]. Reduced NMDA receptor currents by hyperdopaminergia partially depend on dynamin-mediated internalization of GluN2B subunits [162]. Notably, postsynaptic molecules appear to be involved in hypodopominergia-mediated regulation of NMDA receptor currents. Such hypothesis is based on the evidence that the protein phosphatase 2A

(PP2A)- phosphatidylinositol 3-kinase (PI3K)- glycogen synthase kinase-3β (GSK-3β)-βcatenin pathway is implicated in hyperdopamine-D_2 induced dampening of NMDA receptor currents in prefrontal neurons *via* increases in GluN2B endocytosis and decreases in GluN2B gene expression [162]. Accordingly, the hyperdopaminergic state, induced by chronic systemic administration of the dopamine releaser agent GBR12909, increases the amount and phosphorylation of GSK-3β in the PFC [162], thus suggesting an increase in GSK-3β activity under hyperdopaminergic conditions.

A growing body of evidence is thus emerging on the role of PSD proteins in mediating dopamine-glutamate interaction. PSD proteins are thought to modulate dopamine and glutamate receptor trafficking and localization to the surface membranes and their reciprocal interaction. Moreover, PSD proteins may mediate common intracellular signaling pathways for these two neurotransmitters. Therefore, pharmacological manipulation of PSD proteins may represent a future valuable strategy to restore putatively impaired dopamine-glutamate interaction in schizophrenia.

POST-RECEPTOR GLUTAMATERGIC TARGETS FOR NOVEL ANTIPSYCHOTIC STRATEGIES

Since glutamatergic dysfunctions have been implicated in the pathophysiology of schizophrenia, it has been proposed that compounds acting on glutamatergic targets, *i.e*. glutamate receptors, may exert favorable treatment outcomes in schizophrenia patients. Several glutamatergic compounds have been tested in preclinical settings to evaluate their antipsychotic potential. Among these, some have already been tested in clinical trials, whereas others are currently being assessed in ongoing clinical trials, albeit yielding conflicting results [163]. More recently, however, intensive research efforts are being focused on establishing whether antipsychotics may target post-receptor sites of action, such as molecules of the PSD.

Among the different antipsychotics being tested is clozapine. This compound, contrary to haloperidol, increases Shank1a density in dendritic spines, as well as dendritic spine density itself, in rat dissociated hippocampal neurons [164]. Notably, clozapine has been found to be more effective in improving cognitive and negative symptoms than other antipsychotics [1]. Its superior clinical efficacy in the treatment of these symptoms may be partially due to its putative action on dendritic spines and PSD proteins.

Chronic treatment with haloperidol, but not olanzapine, has been reported to reduce the protein amount in the synaptosome subfraction of several receptor and post-receptor glutamatergic molecules, including: GluN1 and GluN2A subunits; the AMPA receptor GluA1 subunit; PSD-95; and CaMKII, whose phosphorylation status and interaction with GluN2B subunit is also affected [165].

Similar lines of research have also confirmed the efficacy of clozapine in boosting cortical hypofunction. More specifically, cortical hypofunction has been suggested as one putative mechanism for schizophrenia symptoms, at least negative and cognitive ones, and glutamatergic perturbation has been considered as a major causative mechanism [166, 167]. Recent research has pointed out that clozapine boosts neuronal activity in the prefrontal cortex by eliciting a functional synergism between the 5-HT_1 receptor, the NMDA receptor, and the CaMKII [100, 168], presumably *via* a CaMKII-mediated recruitment of AMPA receptors to the PSD and *via* an increase in excitatory postsynaptic potentials (EPSP).

Beyond its action in glutamatergic signaling, PSD-95 has also been described to crucially participate in serotonergic signaling. 5-HT_{2A} and 5-HT_{2C} receptors-mediated downstream signaling has been found impaired in PSD-95 knock-out mice. PSD-95 has been demonstrated to regulate trafficking to pyramidal neuron apical dendrites, membrane turnover, and neuronal expression of 5-HT_2 receptors [12, 169]. Hallucinogen-like behaviors by 5-HT_{2A} agonist drugs are lost in mice lacking PSD-95 and the atypical antipsychotic clozapine is unable to revert PCP-induced disruption of the prepulse inhibition [169]. Thus, modulation of PSD-95 expression levels or activity may either represent a future strategy for novel antipsychotic agents or enhance the action of current antipsychotics, particularly of those exhibiting a serotonergic profile.

Phosphodiesterase 10A (PDE10A) is a phosphodiesterase isoform that degrades both cAMP and cGMP and is highly enriched in striatal MSNs [170]. PDE10A appears to participate in the postsynaptic cross-talk among signaling cascades from different receptors, including D_1, D_2 , and glutamatergic receptors. Indeed, administration of PDE10A inhibitors increases phosphorylation of the GluA1 subunit of AMPA receptors in striatal neurons [171]. Evidence shows that PDE10A inhibitors are active in preclinical models of antipsychotic efficacy against positive, negative, and cognitive symptoms [171], suggesting that these compounds may represent putative antipsychotic agents targeting both the glutamatergic and the dopaminergic systems at postsynaptic sites. The preferential cortical phosphodiesterase isoform PDE4 hydrolyzes cAMP and disrupts the Gs protein alpha subunit-coupled cAMP-dependent D_1 receptor intracellular signaling [170]. Intriguingly, the PDE4 inhibitor rolipram is able to exert antipsychotic efficacy in preclinical studies [172] and to modulate phosphorylation of several intracellular targets, including GluA1 and GluN1 [173]. Moreover, rolipram enhances D_1 receptor-mediated signaling in cortical neurons [173]. Therefore, rolipram could exert antipsychotic action by augmenting D_1-receptor mediated and glutamatergic signaling.

Among the PSD members, Homer appears to be another putative target of antipsychotic action. Acute and chronic administration of antipsychotics has consistently been shown to induce expression of the inducible Homer1variant *Homer1a* in cortical and subcortical areas of the rat forebrain [78, 79, 81]. Notably, temporal and spatial patterns of *Homer1a* expression are obviously different among antipsychotics and may depend on the actual perturbation of dopaminergic signaling by each compound. Indeed, it has been demonstrated that *Homer1a* expression in the striatum and, to a lesser extent, in the cortex, is mainly modulated by selective antagonism to D_2 receptors compared to other dopamine receptor subtypes [174]. Among the various

antipsychotics, haloperidol has been found to induce the gene in all striatal subregions [78, 80, 81, 107, 175, 176]. Atypical antipsychotics show two patterns of *Homer1a* expression. Whereas risperidone, olanzapine, and low-dose ziprasidone activate *Homer1 a* only in the lateral striatum [107], high-dose ziprasidone activates it in the whole striatum [81]. By contrast, clozapine, quetiapine, and sertindole are unable to activate the gene in the striatum [80, 176]. Amisulpride showed a unique *Homer1a* preferential induction in the medial striatum [177]. Overall, the discrepant patterns of *Homer1a* expression in the striatum by antipsychotics mirror the ability of each antipsychotic to affect dopaminergic transmission. Notably, *Homer1a* is induced in the striatum by drugs that increase dopamine outflow, such as cocaine, methylphenidate, or GBR12909 [78, 178-180], and by a D_1 receptor agonist [181]. Antipsychotics themselves are known to acutely increase dopamine levels in the striatum after their administration [182]. Therefore, the pattern of *Homer1a* expression could reflect/reveal the actual synaptic levels of dopamine and thus putatively represent a tool for *in vivo* molecular neuroimaging that would closely resemble human PET studies by radiotracers.

Taken together, these studies confirm the hypothesis that PSD proteins may be promising targets for future antipsychotic approaches. Indeed, PSD proteins are at the cross-road of dopamine, glutamate, and serotonin signaling, all of which have been considered dysfunctional in schizophrenia. Targeting PSD proteins may possibly restore the adequate balance between these neurotransmitter systems and directly modulate synaptic plasticity.

DISCUSSION

In this review, we attempted to provide a thoroughly critical appraisal on the role of glutamatergic PSD in schizophrenia pathophysiology, whose relevance has been suggested due to inconsistency in experimental findings on glutamatergic dysfunctions in other sites.

Hypofunction of glutamatergic transmission by NMDA receptors has been considered a valuable model for the pathophysiology of the disease. However, experimental evidence has not fully supported this hypothesis. Indeed, studies on glutamate receptor anomalies have failed to find consistent alterations in schizophrenia patients.

Several methodological limitations may explain such inconsistency. One limitation could be sample collection. Sample selection is indeed one of the most challenging issues in both clinical and genetic research— an issue that is even more relevant for the complex phenotypic presentation of psychiatric diseases [183, 184]. Cases in point of this complexity are glutamatergic dysfunctions. Indeed, these dysfunctions could only underlie specifically defined domains of schizophrenia symptoms, *e.g*. cognitive and negative ones, and not the whole illness. Should this be the case, molecular studies will always fail unless sample selection is restricted according to more stringent and lesion-directed criteria. Other sources of bias in sample selection for molecular studies derive either from duration of pathology, exposure to antipsychotics and concomitant psychotropic medications, or from more technical concerns, including the limited methods for processing postmortem tissues. All of these issues may strongly affect results and cause distortions that are arduous to control preventively and to rule out *ex-post*. Despite the drawbacks from human studies, preclinical reports more consistently indicate that impaired glutamatergic signaling is pivotally implicated in schizophrenia pathophysiology [185, 186].

A growing body of evidence has shown that glutamatergic alterations in schizophrenia could not occur exclusively at the receptor level. Since multiple rare variants of common genes underlie schizophrenia pathophysiology [187], multiple glutamatergic molecules may be implicated in the disease. In these terms, post-receptor molecules, such as those belonging to the PSD, represent compelling candidates as putative causative agents and possible therapeutic targets. Indeed, PSD proteins are implicated in glutamatergic signaling by several biological actions. First, they regulate glutamatergic and non-glutamatergic receptor trafficking and localization within dendritic spine microdomains; second, they physically connect glutamate receptors with intracellular effectors; third, they mediate cross-talk with other signaling systems; fourth, they directly modulate surface and intracellular ion channels and tune Ca^{++} dynamics; finally, they control synaptic architecture and function [12, 94]. A growing number of reports are associating PSD proteins with the neurobiology of schizophrenia and other severe mental diseases, such as bipolar disorder. Impairment of PSD proteins may cause a range of molecular alterations that have been either hypothesized or demonstrated in schizophrenia. These include aberrant receptor trafficking and localization within synapses or disrupted interplay between the glutamatergic and other neurotransmitter systems, such as the dopaminergic system. This range of molecular alterations may ultimately lead to a failure in–synaptic plasticity, which has been considered central to schizophrenia pathophysiology [188, 189].

The recent observation that PSD proteins are modulated by antidopaminergic compounds commonly used in schizophrenia therapy, such as antipsychotics, has further reinforced interest in these molecules. PSD proteins may therefore represent an intracellular hub where dopamine and glutamate may modulate one another reciprocally. Therefore, direct targeting of these molecules may appear to be beneficial in schizophrenia therapy, especially in the treatment of resistant conditions where conventional antipsychotics fail to fully control psychotic symptoms. Despite multiple technical concerns, some recent clinical and preclinical studies have investigated the efficacy of cell permeable peptides (CPP) and small peptide inhibitors (SPI), which may specifically interact with PSD proteins, such as PSD-95 [190, 191]. CPPs are small peptide sequences containing a membrane-permeable sequence allowing entry within cells [192]. CPPs may be biologically active *per se* (this is properly the case of SPIs) or may function as vectors for intracellular delivery of hydrophilic molecules having an intrinsic pharmacological activity [193]. Specifically, SPIs are constituted of a small peptide sequences similar to that of the target proteins, allowing the SPI to compete with the target protein for binding with partners. In recent years, the

possibility to use CPPs and SPIs with therapeutic goals has been explored in several medical fields, ranging from immunology to oncology [194, 195]. In neuroscience, the use of CPPs and SPIs as putative therapeutic devices has received only limited attention at the moment. A cell-permeable peptide designed to inhibit the c-Jun N-terminal kinase action has been used to prevent excitotoxicity and sequelae of stroke [196] and has been hypothesized to block the cell-death signaling cascades implicated in neurodegenerative diseases [197]. Notably, small peptide inhibitors of the PSD-95/NMDA receptor interaction have been described to reduce the severity and size of ischemic area after stroke [190, 191]. Although these studies have been conducted in non-psychiatric settings, they are paving the way to a novel strategy that could putatively be useful in mental disorders, such as schizophrenia. Given the fundamental role of protein-protein interactions in the PSD to control synaptic plasticity and neurotransmitter signaling and the supposed role of PSD proteins in schizophrenia pathophysiology, it can be hypothesized that CPPs and/or SPIs specifically designed to disrupt PSD protein interactions may represent promising upcoming candidate pharmacological tools for the treatment of the disease.

In conclusion, these considerations suggest that in the future post-receptor targeted therapeutic agents could complement and possibly replace conventional antipsychotics, thus improving the overall efficacy and tolerability of current treatments.

CONFLICT OF INTEREST

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