Mol Neurobiol (2012) 46:275–296
DOI 10.1007/s12035-012-8293-6

Calcium-Dependent Networks in Dopamine–Glutamate Interaction: The Role of Postsynaptic Scaffolding Proteins

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Received: 4 April 2012 / Accepted: 21 June 2012 / Published online: 5 July 2012

Abstract Dopamine and glutamate systems are both involved in cognitive, behavioral, and motor processes. Dysfunction of dopamine–glutamate interplay has been suggested in several psychotic diseases, above all in schizophrenia, for which there exists a need for novel medications. Intracellular calcium-dependent transduction pathways are key determinants of dopamine–glutamate interactions, which take place mainly, albeit not exclusively, in the postsynaptic density (PSD), a highly specialized postsynaptic ultrastructure. Stimulation of dopamine and glutamate receptors modulates the gene expression and the function of specific PSD proteins, the "scaffolding" proteins (Homer, Shank, and PSD95), belonging to a complex Ca^{2+}-regulated network that integrates and converges dopamine and glutamate signaling to appropriate nuclear targets. Dysfunction of scaffolding proteins leads to severe impairment of Ca^{2+}-dependent signaling, which may underlie the dopamine–glutamate aberrations putatively implicated in the pathogenesis of psychotic disorders. Antipsychotic therapy has been demonstrated to directly and indirectly affect the neuronal Ca^{2+}-dependent pathways through the modulation of PSD scaffolding proteins, such as Homer, therefore influencing both dopaminergic and glutamatergic functions and enforcing Ca^{2+}-mediated long-term synaptic changes. In this review, we will discuss the role of PSD scaffolding proteins in routing Ca^{2+}-dependent signals to the nucleus. In particular, we will address the implication of PSD scaffolding proteins in the intracellular connections between dopamine and glutamate pathways, which involve both Ca^{2+}-dependent and Ca^{2+}-independent mechanisms. Finally, we will discuss how new strategies for the treatment of psychosis aim at developing antipsychotics that may impact both glutamate and dopamine signaling, and what should be the possible role of PSD scaffolding proteins.

Keywords Postsynaptic density · Homer · PSD95 · Shank · Psychosis · Antipsychotics

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Introduction

Dopamine and glutamate systems are the most important neurotransmission circuitries implicated in the pathogenesis of psychosis. Their manifold interconnections, even with the other neurotransmission systems, control cognitive, behavioral, and motor processes. Thus, from the loss of balance in the complex interplay among these systems could originate the variety of expression of psychotic disorders, such as schizophrenia or bipolar disorder.

In specific brain areas, which have been implicated in the pathophysiology of psychosis (i.e., prefrontal cortex, corpus striatum, and nucleus accumbens), dopamine and glutamate signaling pathways converge on responsive neural populations, such as the striatal medium-sized spiny GABAergic neurons (MSNs) or the cortical GABAergic interneurons, where they interact at postsynaptic level. Deciphering the molecular mechanisms that control the postsynaptic dopamine–glutamate interplay may be crucial to our understanding of the dysfunctions implicated in psychosis, as well as for the development of new therapeutic strategies.

The diverse actions of dopamine are mediated by at least five distinct subtypes of dopamine receptors (DARs), which belong to the G-protein coupled receptors (GPCRs). Two D1-like receptor subtypes (D1 and D5 receptors) couple to the G protein G_s and activate adenylyl cyclase. The D2-like receptors (D2, D3, and D4 receptors) inhibit adenylyl cyclase and activate K^+ channels [1].

On the other hand, glutamate functions are mediated by both ionotropic and metabotropic receptors. The widely distributed ionotropic glutamate receptors are ion channels activated by glutamate and may be divided in subtypes according to postsynaptic currents: *N*-methyl-D-aspartate receptors (NMDARs), 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid receptors (AMPARs), and kainate receptors (reviewed in [2]).

Metabotropic glutamate receptors (mGlu receptors) belong to the seven transmembrane passages receptors superfamily and exert their cellular effects by activating G-protein-dependent pathways [3, 4]. According to their transductional pathways, mGlu receptors can be divided in three groups: group I (mGlu1 and mGlu5 receptors subtypes), whose stimulation leads to Phospholipase C–inositol 1,4,5-trisphosphate (PLC-IP3)–Ca^{2+} pathway activation and increases intracellular calcium; group II (mGlu2 and mGlu3 receptors subtypes); and group III (mGlu4, mGlu6, mGlu7, and mGlu8 receptors subtypes), whose stimulation decreases intracellular calcium concentrations by inhibiting adenylyl cyclase.

Both dopamine and glutamate receptors, indeed, may impact calcium-dependent intracellular signals (reviewed in [5–7]) that are key triggers of the molecular mechanisms underpinning synaptic plasticity, which include both activity-dependent gene transcription and long-term neural adaptations [8].

Among the wide variety of postsynaptic effectors that control calcium intracellular signals are the postsynaptic density (PSD) scaffolding proteins, which play a crucial role in the complex postsynaptic architecture of excitatory synapses (for a review, see [9]), where the most part of signal transduction events take part that lead to the dopamine–glutamate-mediated synaptic plasticity.

The first part of this review provides an overview of the direct and indirect dopamine–glutamate interactions and of the complex mechanisms by which dopamine and glutamate transductional pathways exert their intracellular signaling crosstalk. It will be pointed out the role of postsynaptic density (PSD) scaffolding proteins (Homer, Shank, PSD95) in the control of Ca^{2+}-dependent signaling pathways starting at either dopamine or glutamate receptors. Thus, we will discuss the intrinsic mechanisms that could be putatively implicated in psychotic disorders.

The second part will focus on the implication of PSD scaffolding proteins in dopamine–glutamate dysfunctions underlying major psychiatric disorders, such as schizophrenia. Moreover, we will discuss the possible role of PSD scaffolding proteins in future dopamine–glutamate integrated therapies and the potential implication for the treatment of psychotic disorders.

Dopamine and Glutamate Circuitries Nexus: A Pathophysiology Integrated Model of Psychosis

Dopamine–Glutamate Hypothesis of Psychosis

Over 30 years in psychotic disorders basic investigation have moved the attention from unidirectional models of pathogenesis to multidirectional and integrated ones.

Abnormal dopamine and glutamate functions, as well as abnormal development of dopaminergic and glutamatergic neurons, have been implicated in the pathophysiology of the major psychotic disorders, such as schizophrenia and bipolar disorder [10–15], but the underlying mechanisms are still elusive. Both prefrontal cortex (PFC) and striatum—which have been reported as dysfunctional in psychosis—receive dopaminergic and glutamatergic inputs converging on specific neural populations. The MSNs of striatum, indeed, receive dopaminergic projections from the substantia nigra and ventral tegmental area (VTA) of the midbrain, as well as they receive glutamatergic projections from the PFC [16]. On the other hand, dopamine afferents arising from VTA and glutamate afferents arising from hippocampus, thalamus, amygdala, and other cortical areas commonly target both the pyramidal neurons and the GABA interneurons of prefrontal cortex (reviewed in [17]).

Several studies demonstrated that manipulations of both dopamine and glutamate systems may mimic several symptoms of psychotic disorders [18–20]. For instance, drugs affecting glutamatergic system may reproduce negative and cognitive symptoms of schizophrenia, whereas dopamine agonists principally reproduce certain positive symptoms, such as delusions and hallucinations [19].

Based on the evidence that NMDAR-blocking drugs (such as phencyclidine) could induce psychotic manifestations by impacting dopamine neurotransmission, some authors have proposed that a NMDAR dysfunction could be a primary step in the pathogenesis of psychotic disorders, leading to a subsequent—or concurrent—dopaminergic dysfunction [21–23].

Dopamine and Glutamate Signaling Pathways Converge on Responsive GABAergic Neurons in Both Cortex and Striatum

Several studies demonstrated that dopamine and glutamate receptors co-localize on the same neurons in PFC and striatum, thus posing the basis for their molecular postsynaptic interactions. In the PFC, glutamatergic and dopaminergic afferents have been described to converge on the same dendritic spines of excitatory pyramidal neurons, principally in layer V, forming the so-called “synaptic triads” [24]. D1-like dopamine receptors have been shown to localize, with prevalent postsynaptic distribution, at dendritic

synapses [25], where also D2-like dopamine receptors are located, the D2 receptor subtypes (D2Rs) having a preferential localization at layer V, whereas the D4 receptor subtypes (D4Rs) being broadly distributed [26]. NMDARs and dopamine receptors (DARs) have been described to co-localize in the same postsynaptic spines, providing the basis for their subcellular interaction at synapses (Fig. 1) [27]. The dendritic spines of PFC pyramidal neurons are also enriched with group I and group II mGlu receptors, which have essential roles both in controlling dopamine release and in modulating glutamate influences [28–30]. Nonetheless, both dopamine and glutamate receptors have been reported to co-distribute in GABAergic cortical interneurons [26, 28, 31].

In the striatum, D1-like receptors localize mostly on GABAergic MSNs (i.e., the striatal output neurons), preferentially at postsynaptic level, whereas D2-like receptors are located both at presynaptic level—acting as autoreceptors on dopaminergic terminals and as regulators on glutamatergic afferents—and at postsynaptic level on MSNs (for a review, see [32]). Ionotropic glutamate receptors (NMDARs, AMPARs, and kainate receptors) largely co-localize with dopamine receptors in striatum, both at presynaptic level on dopaminergic and glutamatergic afferents and at postsynaptic level on MSNs, where they control excitatory currents [33–36]. On the other hand, there is a growing interest for metabotropic glutamate receptors distribution in the striatum in recent years because of their close interaction with dopamine receptors. The two group I mGlu receptors subtypes, indeed, have different localizations in dopaminergic striatal synapses, the mGlu1a receptors being primarily presynaptic with regulatory effects, whereas the mGlu5 receptors being essentially postsynaptic with prominent synaptic plasticity functions [37]. Moreover, mGlu1 receptors seem to segregate principally in striatonigral MSNs, which are enriched with D1-like dopamine receptors (the "direct" pathway), whereas mGlu5 receptors are mostly located on striatopallidal MSNs, which are characteristically enriched with D2-like receptors

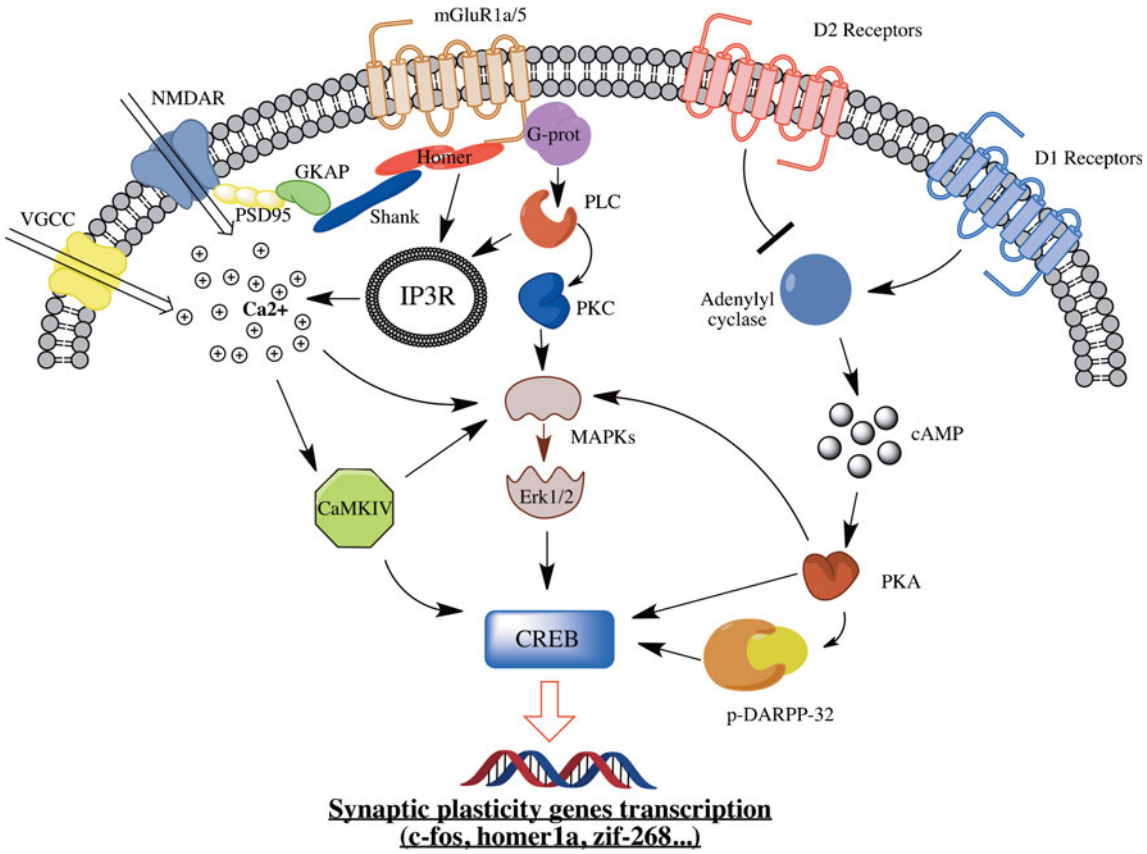

Fig. 1 Dopamine–glutamate postsynaptic interaction. Dopamine and glutamate receptors may activate calcium-dependent and calcium-independent pathways that interact at multiple levels in the postsynaptic density. Postsynaptic scaffolding proteins (Homer, Shank, and PSD95) represent key components of this crosstalk, as well as they may modulate both calcium-dependent and calcium-independent downstream cascades. The transductional pathways converge on effector molecules (*MAPK-Erk1/2-CREB*) that activate the transcription of genes responsible for synaptic plasticity (e.g., *c-fos*, *homer1a*, *zif-268*). *GKAP* guanylate kinase associated protein, *CaMKIV* calcium/calmodulin dependent kinase IV, *PKA* protein kinase A, *PLC* phospholipase C, *PKC* protein kinase C, *IP3R* inositol 1,4,5-trisphosphate receptor, *MAPK* mitogen-activated kinases, *Erk1/2* extracellular signal-regulated kinase, *cAMP* cyclic adenosine monophosphate, *pDARPP-32* dopamine- and cyclic AMP-regulated phosphoprotein of 32 kDa, *CREB* cyclic AMP response element binding

(the "indirect" pathway) [38]. Group II and III mGlu receptors share no less important roles than group I mGlu receptors. They are, indeed, broadly distributed in dopaminergic and glutamatergic striatal terminals, and contribute to regulate dopamine receptors function. Nonetheless, they are largely present on GABAergic and cholinergic striatal interneurons [5].

Therefore, glutamate and dopamine systems interact at multiple levels and their signaling interplays both in cortical and subcortical structures, thus generating an entangled modulatory system that likely is the neuroanatomical substrate for the pathophysiology of psychotic disorders. However, the reciprocal influence of dopamine and glutamate signaling in the neurons where their transductional pathways respectively interact relies on a complex interconnection of intracellular calcium-dependent networks, whose molecular components are still largely elusive.

In the next paragraphs, we will discuss the most recent findings on this issue.

Dopamine–Glutamate Postsynaptic Crossroads: The Calcium-Dependent Synaptic Plasticity Network

As aforementioned, in specific cerebral regions, such as prefrontal cortex and corpus striatum, dopamine and glutamate projections converge at GABAergic responsive neurons. These neurons integrate, through sophisticated intracellular mechanisms, the information originated by the activation of dopamine and glutamate receptors. Thus, dopamine and glutamate interact in PFC and striatum in order to influence neural excitability and to promote synaptic plasticity. The complex modulation of Ca^{2+} intracellular levels as well as the activation of calcium-dependent signaling molecules represents the key substrates for the establishment of synaptic plasticity induced by dopamine–glutamate interplay in both PFC and striatum [39, 40]. Indeed, dopamine D1 and D2 receptors have opposite effects on excitability and calcium levels in neurons. D1 receptors (D1Rs) activate adenylyl cyclase and promote cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA) mechanisms, such as calcium channels activation, whereas D2Rs reduce cAMP formation and PKA activity, thus having the final effect of inhibiting neural excitability (extensively reviewed in [41]). On the other hand, the stimulation of NMDARs leads to direct and indirect activation Ca^{2+}-dependent signaling proteins—such as the calcium-calmodulin-dependent kinase (CaMK) and the PKA—which are essential to synaptic rearrangements [42]. Likewise, mGlu receptors promote calcium-dependent processes through the PLC–IP3 pathway, which modulates intracellular calcium levels (reviewed in [5]).

Besides the differences existing between the molecular mechanisms that underlie calcium-dependent synaptic plasticity in cortical and striatal areas, several studies agree that dopamine signaling is critical to modulate glutamate-induced calcium oscillations in order to promote a correct set up of synaptic plasticity mechanisms, such as in long-term depression (LTD) and long-term potentiation (LTP) [43, 44].

Although a large part of the signaling cascades involved in calcium-dependent synaptic modulation of cortical and striatal dopamine–glutamate synapses have been extensively studied (e.g., adenylyl cyclase, cAMP, PKA, PLC–IP3 etc.), a great deal of evidence suggests a role for PSD scaffolding proteins, which appear as key determinants of the crosstalk between dopamine and glutamate postsynaptic pathways.

Postsynaptic Density Scaffolding Proteins

Postsynaptic Density (PSD) is a specialized structure localized under the postsynaptic membrane at excitatory synapses with an approximate thickness of 30–60 nm and a diameter of 200–500 nm, and a complex structural anatomy [45]. Many proteins, such as ionotropic and metabotropic receptors, receptors-interacting proteins, enzymes, and scaffolding and cytoskeletal proteins, constitute the complex lattice of the PSD [46].

PSD represents a powerful "triage center" where every message reaching the synapse is received, elaborated, and routed to its own final destination (Fig. 2). PSD proteins, indeed, seem to be involved in multiple processes, such as synaptic development and plasticity [47, 48] and control of transductional pathways [49]. Thus, according to several observations, each molecular process putatively involved in postsynaptic dopamine–glutamate interplay should take necessarily place in the PSD, and thereby is controlled by PSD proteins [50]. Many PSD proteins [such as the dopamine- and adenosine 3′,5′ monophosphate (cAMP)-regulated phosphoprotein of 32 kDa (DARPP-32), CaMKII, Neuronal Calcium Sensor-1 (NCS-1), and calcyon] have essential roles in controlling and routing both dopamine and glutamate signalings. However, recent attention is focused on the so-called scaffolding proteins, which constitute an eclectic class of PSD proteins with multiple functions [46].

A large number of studies pointed out the possible role of these proteins in the dopamine–glutamate intracellular crosslinking, and their implication in the pathophysiology of neuropsychiatric disorders originating from dysfunctions in these intricate connections [51–54]. Moreover, PSD scaffolding proteins seem to be essential for calcium-dependent plasticity at excitatory synapses [55].

Hereafter, we will describe the main PSD scaffolding proteins that have been implicated in dopamine–glutamate

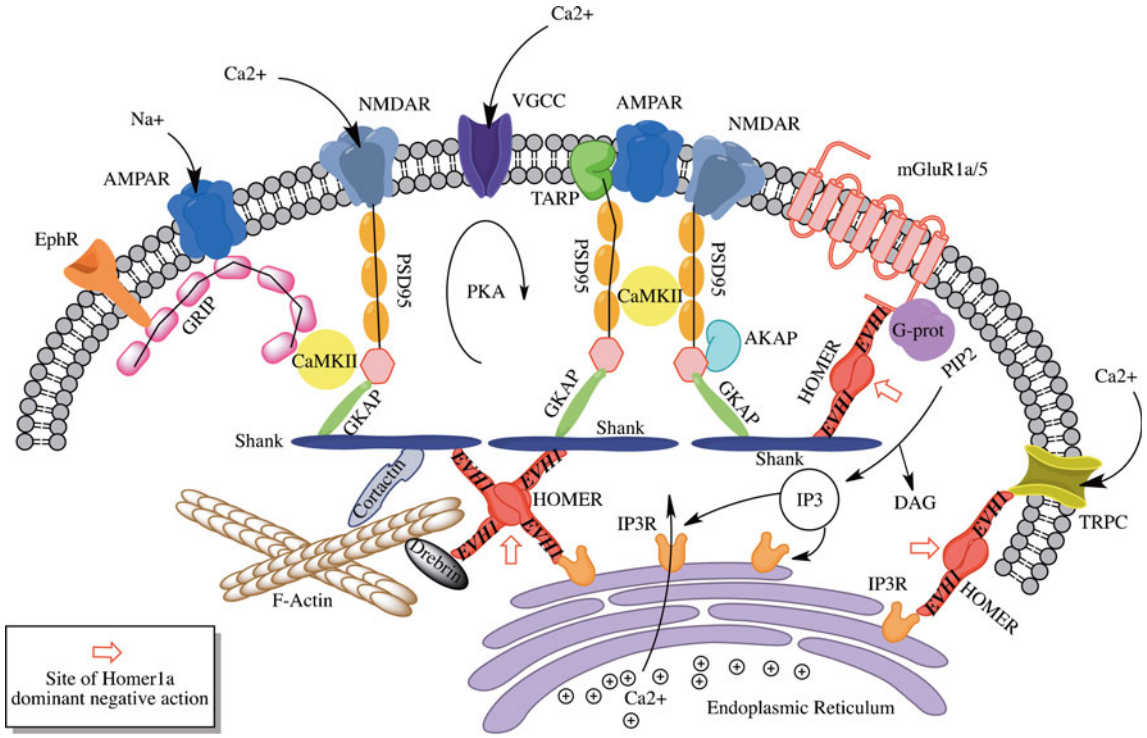

Fig. 2 Postsynaptic scaffolding proteins dynamically organize calcium signaling network in neurons. Through multiple protein–protein interactions, Homer long isoforms, PSD95, and Shank may crosslink transduction pathways starting at both ionotropic (*NMDAR*, *AMPAR*) and metabotropic (*mGlu1a/5*) glutamate receptors. Scaffolding proteins also provide complex interactions between membrane cation channels—such as voltage-gated calcium channels (*VGCC*) and transient receptor potential cation channels (*TRPC*)—with intracellular calcium stores. This network provides the fine-tuning of intracellular calcium signaling. Homer1a, the inducible short form of Homer1 proteins, may be induced by several stimuli. It acts as dominant negative by disassembling long Homers clusters, thereby rearranging the synaptic architecture. Thus, scaffolding proteins may reorganize postsynaptic structure in response to synaptic activity in order to establish short- and long-term neuroplastic changes. *EphR* ephrin receptor, *GRIP* glutamate receptor interacting protein, *GKAP* guanylate kinase associated protein, *CaMKII* calcium/calmodulin-dependent kinase II, *PKA* protein kinase A, *TARP* transmembrane AMPA receptors regulating protein (stargazin), *IP3* inositol 1,4,5-trisphosphate, *IP3R* IP3 receptor, *DAG* diacylglycerol, *PIP2* phosphatidyl-inositol bisphosphate

calcium-dependent plasticity because of their direct connection with glutamate receptor functions in dopaminergic synapses: Homer, PSD95, and Shank.

Homer Family of Proteins: Multimodal Adaptors at Excitatory Synapses

Homer proteins belong to the class of PSD scaffolding proteins, being mainly localized at glutamatergic excitatory synapses [56].

The Homer family comprises three principal members (Homer1, 2, and 3) and several isoforms and splicing variants, encoded by 12 known genes [57, 58].

The multiple isoforms of Homer may be grouped in "long" (Homer1b/c, 2a/b, 3) and "short" proteins (Homer1a and Ania-3), according to the presence of a carboxy-terminal coiled-coil tail, which is absent in the short isoforms (for a review see [9]).

Differently from long isoforms, which are constitutively expressed [57–59], Homer1a and Ania-3 are expressed in an immediate-early gene (IEG)-like fashion and induced by several synaptic activating stimuli [56, 60].

Homer long isoforms may self-associate in multimeric complexes [61] by means of their coiled-coil terminals. Conversely, Homer1a and Ania-3 cannot multimerize and, when induced, they provide to disrupt the other complexes, acting as "dominant negative", thereby influencing synaptic plasticity [62–64].

Homer proteins can interact with many PSD proteins (Fig. 2), such as mGlu receptors, IP3 receptors, ryanodine receptors, transient receptor potential channels (TRPC), cytoskeletal proteins, and the NMDAR-linked protein Shank [56–58, 65–69]. Moreover, Homer long isoforms multimerization is involved in the control of glutamate-mediated postsynaptic adjustments [70, 71] and in glutamatergic synapses development [72].

Conversely, Homer1a is induced by stimuli that modify the synaptic architecture, such as seizure, neurodevelopment, long-term potentiation, and psychostimulant drugs [47, 60, 73, 74].

The multimodal adaptor properties of Homer proteins implicate them in the multiple calcium-dependent processes underpinning synaptic plasticity at excitatory synapses [75]. Indeed, Homer proteins binding may allow the crosstalk between intracellular proteins that belong to the Ca^{2+} signaling network, comprising both ionotropic and metabotropic glutamate receptors as well as Ca^{2+} modulators at intracellular stores, such as inositol 1,4,5-trisphosphate receptors (IP3Rs) and ryanodine receptors (RyRs), in addition to calcium plasma membrane channels [76–78]. Through this action of clustering, scaffolding, and trafficking the most part of the core molecules belonging to the Ca^{2+}-dependent intracellular network, Homer proteins have a crucial role in transducing extracellular stimuli to the nucleus as well as in producing concerted postsynaptic temporal and spatial patterns for efficient functional outputs (see [79]).

Finally, recent evidence suggests that Homer long isoforms are implicated in an additional Ca^{2+}-independent pathway, which is triggered by the combined activation of NMDARs and mGlu receptors and involves the crosstalk between the NMDA receptor-associated protein PSD-95 and the mGlu1/5 receptors-associated protein Homer1b/c [80]. Therefore, given their multifunctional adaptor functions, it is conceivable that Homer proteins may have a significant role in the intracellular cross-linking between dopamine and glutamate pathways.

PSD95: The Main PDZ Scaffolding Protein

PSD95 belongs to the membrane-associated guanylate kinases (MAGUKs), which are modular proteins composed of three N-terminal PDZ domains, followed by a src homology 3 (SH3) domain and a guanylate kinase (GK)-like region. The PDZ domain of PSD95 allows interaction with specific C-terminal Glu-(Ser/Thr)-Xxx-(Val/Ile) recognition motifs, which allow coupling of PSD95 with other signaling molecules (Fig. 2), such as Shank [81], as well as with both G-protein coupled receptors [48] and NMDA ionotropic glutamate receptors [82]. PSD95 interactions mediate stabilization and activity-dependent trafficking of NMDARs [83]. Indeed, early studies reported that, although showing a normal NMDARs localization, PSD95 mutant mice exhibit deficits in LTP, LTD, and spatial learning, suggesting that PSD95 may play a crucial role in linking NMDARs to downstream effectors [84].

PSD95 is also indirectly linked to AMPARs through the interaction with another PSD protein, stargazin [85]. The bidirectional interconnection between PSD95 and stargazin mediates AMPARs targeting to synaptic membrane. Thus, it is possible that a functional linking between NMDARs and AMPARs may occur through PSD95–stargazin complex.

PSD95 may target the phosphokinase A (PKA) to AMPARs via the interaction with the A-kinase anchoring protein (AKAP79). This linkage is necessary for the modulation of AMPA currents by PKA phosphorylation [86]. Moreover, PSD95 has been demonstrated to control also AMPARs surface expression through its own palmitoylation cycles [87].

All the latest studies agree that PSD95 plays a central role in the control of the Ca^{2+}-dependent network that is downstream of glutamate receptors [88, 89], as well as in the signaling of Ca^{2+} and K^{+} channels that are responsible for synaptic excitability [90].

ProSAP/Shank Family of Proteins: Major Docking Stations at PSD

The three members of the ProSAP/Shank family play a master role at excitatory synapses. Shank proteins possess multiple domains that allow protein–protein interactions, such as ankyrin repeats, SH3, PDZ, and SAM (sterile alpha motif) [91]. When Shank is efficiently targeted at synaptic sites through a PDZ-dependent mechanism, it may promote a regulation of synaptic shape and functions, via the interaction with Homer proteins [92]. Moreover, Shank proteins may bridge NMDARs and mGlu receptors via the interaction with GKAP (guanylate kinase-associated protein), and PSD95, thus likely integrating the signaling pathways starting at those two receptors (for review, see [93]).

The docking functions of Shank may putatively allow an entangled coordination of calcium intracellular signaling by glutamate ionotropic and metabotropic receptors (Fig. 2), through the formation of a platform for the assembly of the other PSD protein complexes [94]. Recent evidence, indeed, suggests that the huge homomultimeric sheets formed by Shank proteins may cluster with IP3Rs via Homer interaction, thereby controlling Ca^{2+} intracellular homeostasis [63, 76].

It is clear that Homer, PSD95, and Shank proteins perform master organizing functions in the PSD network, by interconnecting the downstream pathways starting at both ionotropic and metabotropic glutamate receptors, as well as by linking these pathways to the intracellular machinery that controls Ca^{2+} oscillations. In the next sections, we will provide the latest findings examining the role of scaffolding proteins in the interaction between dopamine and glutamate transductional pathways and in their functional connection with the Ca^{2+}-dependent signaling network.

Postsynaptic Modulation of Glutamate NMDA Receptor Currents by Dopamine Receptors

As described above, both PFC and striatum are concurrently targeted by glutamate axons and receive a broad

dopaminergic innervation from mesencephalic neurons of the VTA. In both these regions, a large part of glutamatergic effects are mediated by NMDARs [38, 95], whereas dopaminergic effects are controlled by D1Rs and D2Rs. However, the final output of NMDARs–DARs interplay may diverge according to the brain region in which it occurs. In the PFC, in fact, the subcellular crosslinking between NMDARs and D1Rs may play a crucial role in working memory and cognitive functions [96], whereas in the striatum it is critical for the modulation of motor functions [97, 98], for spatial memory [99], and for appetitive instrumental learning [100].

The first studies on NMDARs–DARs interaction showed that, in both cortical and subcortical regions, the stimulation of D1Rs may potentiate NMDA currents, while D2Rs activation has, if anything, an inhibiting effect [101, 102]. The synergistic effects of NMDARs–DARs co-activation may be blocked by inactivating L-type Ca^{2+} channels, thus providing evidence of the major role of intracellular calcium in dopamine–glutamate interplay. Nonetheless, if D1Rs seem mostly prone to directly interact with NMDARs, the interplay between the ionotropic glutamate receptors and D2Rs occurs even by involving GABA interneurons [103].

NMDARs–D1Rs Interactions

Several mechanisms have been described by which NMDARs and D1Rs may reciprocally interact, ranging from direct physical linking to the crosstalk between their respective signaling pathways. In line with the major role of the cAMP–PKA signaling in D1Rs pathway, a great deal of evidence exists showing that PKA-mediated dephosphorylation of DARPP-32 may induce facilitation of NMDARs [104, 105], these effects being highly dependent on Ca^{2+} concentrations [106]. However, recent studies demonstrated that NMDARs and D1Rs may directly crosstalk, for example through the linkage between D1Rs with NR1 or NR2A subunits of NMDARs [107], or by the recruitment of D1Rs to the membrane after NMDARs activation in a Ca^{2+}-dependent way [108], or even by the increase of NMDARs on the synaptic surface following D1Rs stimulation depending upon the tyrosine kinase Fyn [109].

NMDARs–D2Rs Interactions

The role of D2Rs in synaptic plasticity in cortical and subcortical regions may counterbalance that of D1Rs [110]. Similarly to D1Rs, D2Rs can interact with NMDARs in several ways; for example, D2Rs activation may depress NMDAR currents in striatal [101], hippocampal [111], and cortical [112] neurons. Moreover, D2Rs may not only reduce AMPAR currents in striatum [113] but also decrease AMPARs trafficking through the dephosphorylation of GluR1 subunit [114].

Although a great amount of evidence suggests that the prevailing model of NMDARs–D2Rs interaction, al least in striatal regions, involves the indirect modulation by GABAergic interneurons, which controls glutamatergic inputs [103], in MSNs D2Rs may counteract the facilitation of NMDAR currents induced by D1Rs stimulation (via DARPP-32) through the inhibition of the PKA [95].

Nonetheless, some studies recognized multiple mechanisms in which D2Rs and NMDARs may crosstalk in the same spines, besides PKA modulation. Commonly, D2Rs are coupled to $G_{i/o}$ proteins, leading to inhibition of adenylyl cyclase, yet some evidence suggests that D2Rs stimulation may increase, rather than decrease, intracellular Ca^{2+} levels, thereby activating calcineurin and the mitogen-activated protein kinases (MAPKs) pathway [115]. Other studies reported that, in parallel to cAMP decrease, D2Rs can stimulate the $G_{\beta\gamma}$ subunit, leading to phospholipase Cβ (PLCβ) activation and diacylglycerol (DAG) generation, which stimulates PKC and IP3, and promotes the mobilization of intracellular calcium, as well as inactivation of voltage-gated membrane Ca^{2+} channels, via calcineurin [116].

In addition, D2Rs seems able to transactivate a tyrosine kinase receptor, the platelet-derived growth factor receptor (PDGFR) [111]. PDGFR exerts modulatory effects on NMDAR currents and neurotrophic effects on GABA and dopamine hippocampal neurons [117]. D2Rs cause PDGFR transactivation via $G_{\beta\gamma}$ stimulation. This, in turn, may decrease NMDAR currents through a PLC-mediated mechanism, which increases intracellular Ca^{2+} concentrations.

The Role of PSD Scaffolding Proteins in NMDARs–DARs Coordinated Control of Calcium Signaling

Despite the master role of scaffolding proteins in creating an interface between membrane receptors and intracellular effectors, as well as in fine-tuning Ca^{2+}-dependent downstream to the nucleus, at present a substantial dearth of data exists about their functions in dopamine–glutamate subcellular crosstalk. However, recent studies pointed out the role of some scaffolding PSD proteins in the machinery underlying the interplay between NMDARs and DARs pathways (Fig. 2).

As previously described, the PSD scaffolding protein PSD95 may cluster with NMDARs through its PDZ domain and this linkage seems crucial for NMDARs localization [118]. PSD95 may also interact with D1Rs, thus controlling their trafficking [119]. A recent study by Gu and co-workers suggested that PSD95 could be a core component in the machinery that recruits D1Rs to the membrane when NMDARs are activated [120]. In line with the common observations that the NMDARs–DARs interplay cannot

prescind from PKA/PKC functions, Colledge et al. reported that PSD95 may control the dynamic regulation of phosphokinases by physically docking them to their own substrates, such as glutamate receptors [86]. Furthermore, PSD95 is not only a mere brick of NMDARs–DARs crosstalk but it also can fine-tune their functional interplay. PSD95, indeed, constitutes a multiprotein complex in association with NMDAR and D1R, and may physically counteract the direct linking between the two receptors, thereby inhibiting the reciprocal recruiting and signaling modulation [121]. This should prevent the neuron to be over-stimulated in case of either dopamine or glutamate excessive activity.

At present, the role of the other major PSD scaffolding proteins—such as Homer and Shank—in NMDARs–DARs interplay is not clearly unraveled. However, several studies agree with the view that the entangled network connecting NMDARs and DARs relies on the interaction with some major scaffolding proteins, which allow the indirect contact between membrane receptors and the internal Ca^{2+} stores. For example, a recent work by Azdad et al. demonstrated that D2Rs may modulate NMDAR currents through a specific protein–protein interaction with adenosine A2a receptors (A2aRs), including heteromerization and tightly depending on Shank and Homer functions [122].

A2aRs are G-proteins-coupled receptors (GPCRs) predominantly enriched at enkephalinergic MSNs of striatum, and highly co-localized with D2Rs [123], with reciprocal antagonistic interaction [124]. This interaction depends on the formation of A2aRs–D2Rs heteromers by means of an epitope–epitope electrostatic linkage [125]. The effective decrease in NMDAR currents requires the combined activation of A2aRs and D2Rs. Strikingly, Azdad and co-workers demonstrated that the D2-mediated suppression of NMDAR responses is abolished in absence of Shank and Homer functional crossroads [122]. Shank, indeed, has been reported to physically bridge NMDARs to membrane L-type Ca^{2+} channels (Cav1.3) through the interaction with PSD95 [126]. The functional connection between Shank and Cav1.3 seems necessary for the regulation of calcium plasma membrane currents by D2Rs [127]. In addition, the disruption of Homer binding to Shank also attenuates D2Rs control on Cav1.3 currents. Homer indeed may link Shank to IP3 receptors, thus bringing the Shank–Cav1.3 complex into close proximity to intracellular Ca^{2+} stores [64].

Therefore, all the abovementioned protein–protein interactions constitute an entangled network by means of which D2Rs may functionally control NMDAR currents in the synapse. A master role in this network is played by PSD scaffolding proteins, which help to fine-modulate the calcium intracellular concentrations, providing the substrates for the functions of all the final effectors.

Metabotropic Glutamate Receptors and Dopamine Receptors Postsynaptic Interactions

Localization studies suggest that mGlu receptors play a leading role in dopamine–glutamate calcium-dependent interplay in both cortical and subcortical networks. In the striatum, group I mGlu receptors seem to be located principally on projection neurons and on interneurons, whereas group II and III mGlu receptors exert their activity on presynaptic glutamatergic terminals (reviewed in [5]). This distribution strictly mirrors that of dopamine receptors [37]. In the cortex, mGlu receptors are widely localized and each group shows particular characteristics of distribution: group I mGlu receptors immunoreactivity is found throughout layers III–VI, both on neuronal soma and neuropil; group II/III distribution, instead, exhibits no layer peculiarity [128]. This evidence supports previous observations demonstrating a likely co-distribution of mGlu receptors and dopamine receptors in cortical regions and in cortico-striatal projections [129].

Functional Interactions Between mGlu Receptors and DARs

A great deal of evidence demonstrated that DARs and mGlu receptors may mutually control the release of the respective neurotransmitters [130–133]. Indeed, the activation of group II/III mGlu receptors may reduce dopamine extracellular concentrations in striatal areas, whereas their blockade enhances dopamine release [131]. On the other hand, group I mGlu receptors effects on dopamine release largely depends upon their specific subcellular localization. The two group I mGlu receptors subtypes, namely mGlu1 and mGlu5, display a similar pattern of distribution in the striatum and nucleus accumbens (NAc), being preferentially located either extrasynaptically or at the edges of asymmetric postsynaptic specializations [37]. However, in the striatum a difference exists in the synaptic distribution of mGlu1 and mGlu5, the former being mainly localized presynaptically and the latter postsynaptically at dopaminergic synapses. This peculiar pattern of group I mGlu receptors localization in the basal ganglia may account for the facilitation of dopamine release induced by group I mGlu receptors non-selective agonists in the rat striatum, while no effects have been described by a selective mGlu1 activation in the NAc, likely due to the preferential postsynaptic location of these receptor subtype in this area [134].

According to these observations, several studies have demonstrated that mGlu receptors play a major role in dopamine-mediated processes underpinning learning and cognition, as well as in the expression of behavioral responses to dopaminergic psychostimulants [135–137]. In particular, group II mGlu receptors seem to control the behavioral sensitization and locomotor responses to

amphetamines and cocaine through a direct interplay with dopaminergic receptors [137]. Moreover, knock-out models for group II mGlu receptors display enhanced responsivity to cocaine and impaired motor control [138], thus reinforcing their role in controlling dopamine-mediated behaviors.

By contrast, the role of group I mGlu receptors in the regulation of dopaminergic behaviors is more controversial. Indeed, although both mGlu1 and mGlu5 seem to be able to modulate dopamine striatal release [134], contrasting data exist on the effects of the direct injection of group I mGlu receptors antagonists in nucleus accumbens (NAc) on locomotor response to amphetamines [136, 139]. Furthermore, a recent work described opposite effects of selective mGlu5 agents on the locomotor response induced by NMDARs blockade and amphetamine, the former being enhanced but the latter reduced by mGlu5 agonists [140].

As a further mechanism of interrelation, emerging evidence suggests that G-protein coupled receptors (GPCRs)—such as mGlu receptors and DARs—may directly interact by a protein–protein connection, thereby generating heteromeric complexes which can integrate the downstream respective pathways [141]. This hypothesis was introduced based on the evidence that most GPCRs require dimerization upon agonist activation in order to work (i.e., tyrosine kinases receptors), thus assuming that GPCRs mainly exist as homodimers that may interact with other homodimers to form heterodimers, which could converge their signaling to the intracellular calcium network of proteins [142]. Recent theories postulate the existence of receptor–receptor interactions within clusters of multiple topographically ordered receptors of different types, called "receptors mosaics" [143]. Depending upon the reciprocal interactions, as well as the affinities and the ligand concentrations, the mosaics may display different functions—although being formed by the same components—in distinct brain areas.

The existence of adenosine A2a/dopamine D2 receptors mosaics in the striatopallidal GABA neurons has been well established and is at the base of the possible use of A2a agonists (i.e., caffeine) for the treatment of schizophrenia [144]. Based on the current dopamine–glutamate hypothesis of schizophrenia (which states that the meso-limbic dopamine neurons are hyperactive due to NMDARs cortical hypofunction), the existence of striatal A2aR/D2R mosaics with antagonistic interactions provides the possibility of using A2aRs agonists in order to reduce the D2Rs agonists binding affinity [145]. This should reinforce a concurrent antipsychotic therapy. Furthermore, several studies demonstrated that the combined activation of A2aRs and mGlu5 receptors may synergistically reduce the affinity of D2Rs binding sites [146] and that A2aRs and mGlu5 receptors may co-localize in striatal neurons cultures [147], as well as they may synergistically act on *c-fos* expression and ERK phosphorylation [148].

These observations indicate the existence of A2a/D2/mGlu5 receptors mosaics in striatopallidal GABA neurons with A2aR/mGlu5 synergistically antagonizing D2Rs binding and signaling. Recently, these higher-order oligomers have been demonstrated in rat striatum native tissues [149], although some concerns remain still to elucidate. D2Rs, indeed, negatively modulate Ca^{2+} signaling in striatal neurons via a PKA-mediated mechanism, which is counteracted by activation of A2aRs in the same neurons [150]. However, a lack of synergistic A2aRs/mGlu5 interaction on Ca^{2+} signaling has been observed [151], though both these GPCRs may induce an increase in intracellular calcium concentrations through PLC-IP3 pathway activation [152].

mGlu Receptors and DARs Molecular Interactions in Calcium-Dependent Synaptic Plasticity

The abovementioned observations contribute to design a complex signaling framework in which both dopamine and metabotropic glutamate receptors cooperate in GABAergic neurons in order to induce calcium-dependent long-term synaptic changes at cortical or striatal excitatory synapses (Fig. 1), which represent the molecular substrates for goal-directed cognitive and learning processes as well as for the pathophysiology of psychotic disorders.

A large number of studies agree that mGlu receptors–DARs coordinated signaling is implicated in both long-term potentiation (LTP) and long-term depression (LTD), which are the prominent forms of long-term synaptic plasticity in cortical and striatal circuits ([40, 153] for review). Both LTP and LTD require high levels of intracellular calcium, though these are *per se* not sufficient to induce long-term neural adaptations since the combined activation of D1Rs/D2Rs and mGlu receptors has been reported to be crucial, at least in striatum [154–157]. Specifically, the induction of LTP in striatum selectively requires mGlu receptors activation and is inhibited by D1R/D5R antagonists [158]. Moreover, a recent study reported that adenosine A2a receptors (A2aRs) activation seems to be necessary for LTP establishing in a subset of striatal neurons, providing subtle differences in the synaptic rearrangements among distinct subgroups of MSNs [159]. In cortical areas, LTP establishment also requires an increase in the number of AMPARs on cell surface, which depends upon the interaction with the PSD scaffolding protein PSD95 [160].

On the other hand, the mechanisms involved in LTD induction rely on postsynaptic calcium-dependent modifications that implicate multiple pathways activation and, differently from LTP, have their final output in a retrograde presynaptic efficacy decrease. Although some studies reported that a strong glutamatergic stimulus may induce

LTD independent of dopamine signaling [153], in normal conditions both the activation of group I mGlu receptors and the mild depolarization induced by D2Rs are necessary to establish LTD, besides a massive extracellular Ca^{2+} influx via NMDARs [158]. This combined dopamine–glutamate signaling would lead to a subsequent L-type Ca^{2+} channels activation (with further calcium influx), which seems to be essential to induce a retrograde release of endocannabinoids from postsynaptic neurons, thereby promoting the decrease in presynaptic strength [161].

All these observations suggest that a postsynaptic interplay may exist between mGlu receptors and DARs transductional pathways, as described for NMDARs–DARs. The mechanisms underlying this interplay are likely to be complex and mostly unraveled, and rely on various hypotheses, such as the direct protein–protein interaction, the crosslinkings among proteins belonging to the respective downstream pathways (i.e., postsynaptic adaptors), or the concurrent activation of mGlu receptors and DARs due to extrasynaptic diffusion of both dopamine and glutamate. Regarding this latter mechanism, it is worth noting that some studies demonstrated the expression of specific mRNAs for vesicular glutamate transporter in midbrain dopaminergic neurons [162], as well as the possible release of glutamate onto striatal neurons by midbrain dopamine neurons [163]. Therefore, the possibility of dopamine and glutamate co-release should be kept in mind while examining the putative source of mGlu receptors–DARs postsynaptic cooperation in striatal neurons. Furthermore, although dopaminergic and glutamatergic terminals do not have direct contacts in the striatum, their boutons closely converge on striatal medium-sized spiny neurons [164] and some studies demonstrated that dopamine spillover from nigrostriatal synapses may activate dopamine presynaptic receptors on the neighboring glutamate afferents from the cortex, thus regulating glutamate release in striatum [165, 166]. Similarly, glutamate spillover from corticostriatal afferents may regulate dopamine release from nigrostriatal synapses through mGlu1 receptors [167].

Intracellular Effectors of mGlu Receptors–DARs Interaction: Role of PSD Scaffolding Proteins

Although the second messengers involved in the postsynaptic cooperation of DARs and mGlu receptors are still to be dissected, a large number of studies demonstrated that dopamine and metabotropic glutamate receptors co-activation leads to synergistic or additive increase in ERK functions, which is a master actor of long-term neural adaptations finalized to goal-directed behaviors (for an extensive review, see [44]).

All these findings indicate that mGlu receptors and DARs postsynaptically interplay and commonly target the intracellular Ca^{2+}-dependent protein network in order to fine-modulate a complex integrated downstream signaling that is substrate for synaptic plasticity (Fig. 2). Furthermore, mGlu receptors are specifically required to induce striatal gene expression of transcription factors (*c-fos* and *zif268*), which are crucial for establishing dopamine-mediated long-term synaptic rearrangements [168].

Considering the master role of postsynaptic scaffolding proteins in regulating the crosstalk among different Ca^{2+}-dependent pathways, it may be conceivable that PSD95, Homer, and Shank may participate in the mGlu receptors/DARs interconnections.

Although a substantial dearth of data still exists on this issue, PSD scaffolding proteins are widely recognized as postsynaptic adaptors along the transductional pathways starting at mGlu receptors. Homer proteins, indeed, have the prominent function of anchoring mGlu1/5 receptors at excitatory synapses [56]. Because of their capability of self-assembly, Homer proteins may organize mGlu receptors into multiprotein complexes in the PSD, and link mGlu receptors to specific postsynaptic signaling pathways in order to generate a signaling machinery that crosstalks with other receptors pathways (see [9, 51]). Homer proteins interact with mGlu receptors to modulate their membrane trafficking and clustering [169, 170] as well as their coupling to IP3Rs [67]. Moreover, the N-type calcium channels modulation by group I mGlu receptors is closely dependent upon the relative ratio between Homer short and long isoforms, thereby being impaired when Homer1a is overexpressed [171]. These findings suggest a model in which Homer proteins exert a master control on mGlu receptors-mediated calcium signaling. Homer long proteins, indeed, would act as a scaffold to localize group I mGlu receptors in the membrane, nearby IP3Rs, to which they are coupled in order to facilitate their activation and the modulation of intracellular Ca^{2+} concentrations. By contrast, when activated, Homer short proteins would promote mGlu receptors–IP3Rs uncoupling and the switch to a IP3Rs-independent calcium signaling through the coupling of mGlu receptors to the membrane N-type Ca^{2+} channels and M-type potassium channels.

Recently, Homer proteins have been also reported to form a central signaling pathway linking mGlu receptors to ERK1/2 in a calcium-independent manner [172]. Moreover, a crucial role of Homer has been described for mGlu receptors-mediated LTD induction in hippocampus [173], as well as for mGlu receptors-based homeostatic scaling synaptic plasticity [174]. Indeed, Homer1a/Homer1b/c ratio and mGlu5 receptors binding seems to be essential to normal cognitive functions and learning [175], as well as it plays a crucial role in the pathophysiology of diseases in which cognition is impaired [176].

Although still largely unraveled, the molecular mechanisms by which Homer scaffolding proteins might be able to

crosslink mGlu receptors to DARs intracellular pathways could be inferred from several reports. Indeed, both mGlu receptors and Homer proteins have been implicated in the behavioral plasticity mediated by dopaminergic drugs of abuse [53, 177]. Recent data reported that the synaptosomal levels of mGlu5 receptors were significantly reduced in the nucleus accumbens (NAc) shell of animal models following extinction of cocaine self-administration [178], with a concurrent reduction of Homer1b/c and PSD95 levels. This supports the view that these two scaffolding proteins play essential roles in the glutamatergic neuroplastic adaptations associated to the extinction of dopaminergic drug-seeking behavior. Similarly, in response to repeated cocaine administration, levels of mGlu1a receptors and Homer2a/b seem to be downregulated in the NAc shell and upregulated in prefrontal cortex [179]. Homer2 overexpression seems to be further implicated in dopamine- and glutamate-mediated synaptic persistent rearrangements in NAc following chronic alcohol intake [180].

Recent findings of altered levels of Homer1b/c and PSD95 in the glutamatergic PSD of postmortem amygdala of heroin and cocaine abusers seem to confirm the above pre-clinical data [181].

Studies in MPTP-treated wild-type (WT) and Homer-mutant mice have confirmed the involvement of Homer proteins in the modulation of mGlu receptors signaling following dopaminergic perturbation [182]. Indeed, in MPTP-treated WT mice, both Homer1a and mGlu5 receptors striatal levels were reduced, suggesting that dopamine striatal afferents may modulate mGlu receptors function through the regulation of their trafficking/localization by acting on Homer proteins, which are essential to stabilize mGlu receptors in the plasma membrane of striatal neurons. Furthermore, both the subsynaptic localization of mGlu5 receptors and their glial expression displayed complex changes in MPTP-treated and Homer knock-out mice, providing evidence for elaborated regulatory changes of mGlu receptors topography by dopamine, likely mediated by Homer proteins.

Finally, multiple findings support the view that mGlu receptors and DARs signaling may crosstalk through PSD scaffolding proteins in order to converge on the modulation of plasticity genes. Indeed, mGlu5 receptors activation promotes two parallel and complementary Ca^{2+}-dependent—via phosphoinositide—and Ca^{2+}-independent—via Homer1b/c—pathways in order to activate ERK1/2 phosphorylation and the subsequent CREB transcriptional activity of *c-fos* gene [172]. Also, it is well established that dopaminergic drugs, such as amphetamines, may promote CREB phosphorylation via D1Rs and *c-fos* transcription, and that the blockade of group I mGlu receptors is capable to attenuate these effects [183–185]. On the other hand, several studies reported that cocaine and amphetamines strongly affect Homer genes expression [186, 187] by specifically acting on D1Rs [188]. Since D1Rs and mGlu receptors closely interplay in striatal MSNs, it is feasible that Homer proteins play a master role in this interaction, although further studies will need to define the specificity of the function of Homer in integrating mGlu receptors and DARs signals and gene expression.

Targeting the Dopamine–Glutamate Interaction: Role of PSD Scaffolding Proteins in the New Strategies for Antipsychotic Medications

Among the wide range of molecular dysfunctions reported in psychosis, the unifying element seems to be the pervasive underlying calcium signaling abnormalities [189, 190]. Dysfunctions in calcium homeostasis largely depend upon disruption of intracellular networks that provide connections among the principal signaling pathways implicated in schizophrenia and bipolar disorder—i.e., dopamine and glutamate. A major role in these interactions is played by PSD scaffolding proteins, which have been extensively implicated in the pathophysiology of psychotic disorders as well as in the mechanisms of action of antipsychotics, and that could represent valuable candidates for new therapeutic strategies based on a dopamine–glutamate integrated targeting.

PSD Scaffolding Proteins Implication in Psychosis

Several studies (summarized in Table 1) have pointed out the putative implication of PSD scaffolding proteins—as well as of genes encoding for them—in the pathophysiology of psychotic disorders that rely on a substantial dysfunction in dopamine–glutamate synaptic interplay, such as schizophrenia or bipolar disorder.

Although PSD95 is required for trafficking of NMDARs to dendritic spines [191], knock-out mice for PSD95 display no alterations in the number of NMDARs at the synapse, whereas they exhibit abnormal LTP and learning deficits, as well as behavioral features predictive of schizophrenia in animal models [84]. Recently, a newly developed animal model of psychosis, based on growth factors signaling knock-out, has been reported to show concurrent alterations in dopamine and serotonin levels in the brain, reduction in NMDARs subunits and PSD95, and decreases in calcium intracellular signaling, as well as behavioral abnormalities reverted by antipsychotic therapy [192].

In agreement with these studies in animal models, investigations in postmortem human brains of patients with schizophrenia or bipolar disorder demonstrated only modest changes in NMDARs subunits expression, whereas robust changes in PSD95 levels were found in the thalamus, cortex,

Table 1 Preclinical and clinical studies implicating PSD scaffolding proteins in the pathophysiology of psychotic disorders [54, 84, 192, 194–196, 199–201, 204, 205, 211, 232–237]

	Description of findings	Reference
PSD95	Knock-out mice exhibit impaired spatial learning and enhanced long-term potentiation. No alterations in NMDA localization and functions	[84]
	Knock-out animals for heparin-binding epidermal growth factor (a neurotrophic factor implicated in schizophrenia) exhibit decreases in dopamine and serotonin levels, reduction in NR1 subunit of NMDAR, and decreases in PSD95	[192]
	NR1 subunit of NMDAR is down-regulated in dopaminergic neurons of the substantia nigra in postmortem brains of schizophrenic patients, while there are no alterations in AMPA subunits. PSD95 is overexpressed	[232]
	PSD95 expression is reduced in striatal regions of postmortem brains of bipolar patients	[195]
	Hippocampal dentate gyrus and orbitofrontal cortex of schizophrenic and bipolar disorder postmortem brains show lower levels of PSD95 expression, yet there are no alterations in NMDARs subunits	[196]
	NR1 subunit of NMDARs is increased in cingulate cortex of elderly schizophrenics postmortem brains. Increased transcription but decreased protein levels of PSD95 are found in the same brain region	[233]
	Increased expression of NR2B subunit of NMDARs and decreased PSD95 expression in postmortem thalamus of schizophrenic and bipolar patients	[194]
	Decreased phosphorylation of PSD95 and NR2B subunit of NMDARs in cingulate cortex and increased phosphorylation of PSD95 and NR2B in dorsolateral prefrontal cortex of postmortem schizophrenic brains	[234]
Homer1	Homer1 knock-out mice exhibit deficits in spatial learning tests, impaired prepulse inhibition and other behavioral abnormalities predictive of schizophrenia	[54]
	In Homer1 knock-out mice, the overexpression in prefrontal cortex of either the short isoform Homer1a or the long isoform Homer1c reverses behavioral abnormalities, sensitivity to cocaine, and glutamate cortical content	[235]
	In a fragile X syndrome mouse model, Homer scaffolding functions are disrupted, providing abnormal mGlu5 receptors distribution. Genetic deletion of Homer1a restores mGlu5-Homer scaffolds and corrects some phenotypes	[176]
	A SNP mutation in Homer1 gene is associated to neuropsychiatric phenotypes, such as schizophrenia	[199]
	SNP analysis in a multi-stage association study reveals a significant association of Homer2 gene with schizophrenia	[201]
	Two Homer1 polymorphisms are associated with subscales response to Positive And Negative Symptoms Scale (PANSS) by schizophrenic patients at baseline et after 4 weeks of antipsychotic treatment	[200]
Shank	The T allele of Shank1 promoter is associated with impaired auditory working memory and digit span in schizophrenic patients	[211]
	Two de novo copy number variations of Shank2 are associated with mental retardation and autism, and are responsible for impaired dendrite spine morphogenesis	[204, 205]
	Shank3 mutant mice have altered expression of Homer1b/c protein, abnormal dendritic spine morphogenesis, and dysfunctional long-term potentiation, as well as locomotor impairment	[236]
	Shank1 null mutant mice exhibit aberrant ultrasonic vocalization and scent marks, with communication deficits	[237]

and striatum [193–195]. Furthermore, lower levels of PSD95 gene expression have been found in hippocampal subregions of postmortem brains of schizophrenic or bipolar patients, whereas non-significant changes have been noticed in NMDARs expression [196]. These findings suggest that the glutamatergic alterations in psychotic disorders may rely on the abnormal expression of PSD proteins known to be essential for glutamate functions, but not on aberrant glutamate receptors distribution. However, no association with PSD95 polymorphisms has been found in schizophrenic patients [197].

A disruption in the complex protein platform composed by Homer and other PSD proteins (Shank, GKAP, and PSD95) may impair the fine-tuning functions of dopamine–glutamate subcellular calcium-dependent interplay at multiple levels.

Homer1 knock-out mice (but not Homer2) display behavioral phenotypes consistent with an animal model of schizophrenia [54], exhibiting deficits in pre-pulse inhibition tests and increased response to phencyclidine, both effects reverted by antipsychotics. Moreover, Homer proteins have been implicated in dopaminergic drug-induced neuroplastic changes [198].

Early human studies identified an association between Homer1 polymorphisms and the susceptibility to neuropsychiatric disorders [199]. Recently, Homer1 polymorphisms have been specifically associated with psychopathology and treatment response in schizophrenic patients [200]. Similarly, a role for Homer2 in schizophrenia has been reported in a multi-stage association study [201].

Also, impairment in Shank functions has been associated with dysfunctions in routing signals to the nucleus and in synaptic plasticity. Interestingly, in the last years several mutations have been identified in the three members of the Shank family (Shank1, Shank2, and Shank3). Although they were associated to different disorders, all these mutations share the common feature of inducing a pervasive impairment in cognitive and learning functions. Indeed, mutations in Shank3 have been correlated to autism spectrum disorders [202, 203]; Shank2 mutations have been

identified in mental retardation and autism [204–206]; and last, all Shanks have been implicated in Alzheimer disease [207–209]. A recent work by Huber et al. demonstrated that disrupted Homer scaffolds are also implicated in the abnormal mGlu5 receptors functions in a mouse model of Fragile X Syndrome, thereby providing a further role for Homer scaffolding proteins in the correct establishment of cortical functions underlying cognitive processes [176]. This evidence could provide additional avenue of investigations on the mechanisms of action of antipsychotic drugs, considering the use of antipsychotics in cognitive dysfunctional autistic children.

Two mutations in Shank3 have been associated with schizophrenia [210] and a mutation in Shank1 promoter leads to significant impairment in auditory working memory in schizophrenic patients and in patients at risk of psychosis [211]. Reverse translational studies demonstrated also that mice lacking Shank3 C terminus exhibit behavioral patterns predictable of psychosis [212].

PSD Modulation by Antipsychotics: Possible Future Tools to Target the Calcium-Dependent Postsynaptic Network Beyond Dopamine and Glutamate Receptors

As previously discussed, the concurrent impairment of catecholaminergic and excitatory neurotransmission, as well as a substantial dysbalance in dopamine–glutamate interplay, have been currently identified as the core molecular mechanisms underlying the symptoms of psychotic disorders, above all cognitive decline and attention-learning deficits. Such noxious biological events have been well described to progressively impair the entangled intracellular Ca^{2+} signaling, which constitutes the key substrate for synaptic plasticity in brain areas implicated in the pathophysiology of psychotic disorders. Moreover, according to the most recent theories, the calcium homeostasis and cellular metabolism dysbalances may represent the prominent underlying dysfunctions in psychotic disorders [213]. Nevertheless, the levels of the intracellular calcium-regulating biomolecule inositol trisphosphate (IP3), an end-product of dopamine receptors pathway, have been associated with prefrontal working memory functions in primates [214].

Therefore, all researches in last decades tried to seek out for possible new candidates for the pharmacotherapy of psychosis, possibly targeting the core molecular components of dopamine–glutamate intracellular cross-talking pathways.

Both dopaminergic agonists (e.g., cocaine) and dopamine antagonists (e.g., raclopride) are known to modulate cortical and striatal intracellular calcium concentrations (as a marker of neural activation) in peculiar ways, according to their relative affinities for either D1Rs or D2Rs, and hence to their specificity for neuronal subpopulations expressing either of the two dopamine receptors [215].

Atypical antipsychotics, indeed, have been reported to facilitate NMDAR-mediated calcium responses in cortical areas, thereby demonstrating a higher efficacy on cognitive symptoms than typical antipsychotics, which do not share these properties [216, 217]. For instance, recent studies demonstrated that the prototypical atypical antipsychotic clozapine—but not the typical antipsychotic haloperidol—may improve NMDAR evoked currents in prefrontal cortex, these effects being dependent on 5HT1a serotonin receptor-mediated activation of CaMKII, which in turn binds to NR2B subunit of NMDAR to become constitutively activated, thereby boosting Ca^{2+}-dependent excitatory postsynaptic potentials [218]. Moreover, 5HT1a receptor affinity seems to be responsible also for the reversal of phencyclidine-induced cortical impairment by clozapine [219].

Based on this evidence, new compounds have been developed, which—in addition to their dopaminergic effects—strongly modulate glutamate-mediated calcium currents in cortical areas. For instance, Lurasidone, a newly developed antipsychotic with high affinities to 5HT1a, 5HT2a, 5HT7 serotonin receptors and D2Rs, has been demonstrated to enhance NMDAR-mediated currents through a significant increase of NMDARs surface expression in cortical synapses, possibly due to 5HT7 receptors affinity [220]. Another new antipsychotic, Asenapine, with a broad affinity for serotonin and dopamine receptors, has been demonstrated to influence NMDAR cortical currents by acting on D1Rs and 5HT6 serotonin receptors [221].

However, the possibility of addressing the unmeet needs for the treatment of complex disorders, such as schizophrenia or bipolar disorder, provides clear reasons to further investigate the molecular mechanisms that underlie antipsychotic therapies, thus aiming at developing new strategies to directly target the molecules considered as major actors of the dopamine–glutamate calcium-dependent network, beyond dopamine and glutamate receptors.

Although a substantial dearth of data still exists on this issue, antipsychotics are far back known to affect the expression of multiple genes in the brain, an effect that is believed to lead to plastic changes in synaptic structures and function [222]. Among these genes, antipsychotics have been reported to modulate the expression of genes encoding for PSD scaffolding proteins, thereby putatively influencing in a direct way the synaptic architecture as well as the Ca^{2+}-dependent crosstalk among dopamine and glutamate transductional pathways.

For instance antipsychotic therapy has been reported to modulate *PSD95* gene expression differentially in cortical and striatal areas [223, 224], probably due to the neuroplastic changes triggered by antipsychotics in their sites of action.

Nevertheless, recent findings reported that, besides its proper role in scaffolding the postsynaptic components of glutamatergic signaling, PSD95 is also crucial for the functions of atypical antipsychotics at 5HT2a and 5HT2c serotonin receptors, by promoting their trafficking and dendritic stabilizing. Therefore, in the absence of *PSD95*, both 5HT2a and 5HT2c receptors exhibit a significant decrease in their downstream signaling, and antipsychotics with affinities for these receptors (such as clozapine) are unable to mediate their effects in animal models of psychosis [225].

A large amount of studies exist examining the role of *Homer* genes in antipsychotic mechanisms of action. *Homer1a* gene, which is induced in a IEG-like fashion and is crucial to fine-tune the calcium-dependent synaptic rearrangements mediated by mGlu receptors, is differentially modulated by typical and atypical antipsychotics, with a pattern of expression closely related to the receptor profile exhibited by each antipsychotic and to its preferential site of action, as well as to its propensity to induce extrapyramidal symptoms [60, 74, 226]. Moreover, recent experiments stated that the induction of *Homer1a* gene expression is directly related to D2Rs blockade [227] and to D1Rs activation [188].

Since the *Homer1* IEG isoform acts as a dominant negative, which modifies synaptic architecture, redistributes long Homers, alters synaptic transmission, and disrupts long Homers clusters (with the subsequent disruption of crosslinkings between NMDARs and mGlu receptors as well as with calcium signaling proteins, such as IP3Rs), the modulation of *Homer1a* by APDs indicates that deep postsynaptic rearrangements in the dopamine–glutamate calcium-dependent interplaying network are induced by both acute and chronic antipsychotic therapy. Furthermore, Homer1 knock-out animals have been demonstrated to be insensitive to the glutamate cortical hyperactivity induced by cocaine and to display psychotic behaviors that could be reverted by haloperidol [54]. Recent studies implicated Homer genes also in the molecular pathways activated by mood stabilizers, as well as demonstrated their role in the crosslinkings between transductional pathways stimulated by the combined administration of antipsychotics and mood stabilizers in an animal model of prolonged co-treatment [228, 229].

All these observations implicate Homer proteins in the modulation of dopamine–glutamate interaction by antipsychotics, as well as in the pathophysiology of psychotic disorders. Moreover, recent data point to Homer involvement in serotonin neurotransmission modulation by antipsychotics [223, 230].

As a further confirmation of the master role of PSD proteins in glutamate-mediated calcium signaling regulation by antipsychotics, recent studies observed that clozapine may differentially modulate dendritic spines formation and synaptogenesis in rat hippocampus through a peculiar impact on *Shank1* expression [231].

Conclusions

In conclusion, PSD scaffolding proteins represent key components of the calcium-dependent postsynaptic network that underlie the crosstalk between dopaminergic and glutamatergic signaling pathways.

Through their multiple protein–protein interactions, Homer, PSD95, and Shank may modulate calcium signaling in order to establish correct long-term synaptic changes triggered by concurrent activation of dopamine and glutamate receptors. Nonetheless, PSD scaffolding proteins are critically involved in the fine-tuning of the reciprocal regulation exerted by dopamine and glutamate receptors on each other downstream cascades.

Thus, it is likely conceivable that PSD scaffolding proteins could be implicated in the pathophysiology of neuropsychiatric disorders that rely on a dysfunctional dopamine–glutamate interaction, which leads to an impairment of the calcium intracellular signaling.

Since the development of novel treatments for psychotic disorders needs further understanding of the core molecular substrates of the underlying dopamine–glutamate dysfunctions, the deeper investigation of PSD scaffolding proteins functions and their involvement in antipsychotic therapies may provide a valuable tool to develop future strategies aiming at a more complete dopamine–glutamate targeted treatment of psychotic disorders.

Acknowledgment We would like to acknowledge Dr. Carmela Dell'Aversano for her helpful suggestions on the first draft of the manuscript.

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Conflict of Interest The authors declare that they have no conflict of interest.

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