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MODULATION OF BEHAVIOR BY SCAFFOLDING PROTEINS OF THE POST-SYNAPTIC DENSITY

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Abstract

Scaffolding proteins of the neuronal post-synaptic density (PSD) are principal organizers of glutamatergic neurotransmission that bring together glutamate receptors and signaling molecules at discrete synaptic locations. Genetic alterations of individual PSD scaffolds therefore disrupt the function of entire multiprotein modules rather than a single glutamatergic mechanism, and thus induce a range of molecular and structural abnormalities in affected neurons. Despite such broad molecular consequences, knockout, knockdown, or knockin of glutamate receptor scaffolds typically affect a subset of specific behaviors and thereby mold and specialize the actions of the ubiquitous glutamatergic neurotransmitter system. Approaches designed to control the function of neuronal scaffolds may therefore have high potential to restore behavioral morbidities and comorbidities in patients with psychiatric disorders. Here we summarize a series of experiments with genetically modified mice revealing the roles of main N-methyl-D-aspartate (NMDA) and group I metabotropic glutamate (mGluR1/5) receptor scaffolds in behavior, discuss the clinical implications of the findings, and propose future research directions.

Keywords

glutamate receptor; scaffold; behavior; psychiatric disorders

1. Introduction

About 60–70% of neurotransmission in the brain is excitatory and mediated by the amino acid glutamate. By acting through three classes of ionotropic receptors and three classes of metabotropic receptors, each containing a multitude of subunits, glutamate affects almost every aspect of brain function, including complex behavior (Choudhury, Lahiri, & Rajamma, 2012; Lipsky & Goldman, 2003). Yet, there is specificity to glutamate actions conferred by receptor subunits, their neuroanatomical localization (Mori & Mishina, 2003), or activation within a particular monoaminergic system (Zweifel, Argilli, Bonci, & Palmiter,

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2008). Another level of distinction is achieved by a class of molecules known as docking or scaffolding proteins. Scaffolds of excitatory neurons are localized at the PSD, a specialized matrix of postsynaptic terminals, where they play a critical role in glutamatergic neurotransmission. Scaffolding proteins contain domains that constrain their interactions to subsets of molecules and thereby form postsynaptic complexes with specific functions. Typically, such complexes include surface and intracellular receptors, adhesion molecules, kinases, phosphatases, small GTPases, and the actin cytoskeleton (Sheng & Hoogenraad, 2007). By bringing together and organizing these different components of glutamate receptor complexes throughout the development and adulthood, scaffold molecules regulate glutamate receptor trafficking and signaling, dendritic structure and function, synaptic plasticity, and behavior (Fagni, Ango, Perroy, & Bockaert, 2004; van Zundert, Yoshii, & Constantine-Paton, 2004).

The roles of PSD scaffolds in molecular and cellular processes within the central nervous system (CNS) have been recently reviewed in depth (Emes & Grant, 2012; Verpelli, Schmeisser, Sala, & Boeckers, 2012; Zheng, Seabold, Horak, & Petralia, 2011). Here we present an overview of their behavior roles revealed by studies with genetically modified mice, focusing on the NMDAR and mGluR1/5 scaffolds of the MAGUK (membrane-associated guanylyl kinase), Shank (SH3 domain and ankyrin repeat-containing protein) and Homer families (Figure 1). Together with human studies, these mouse genetic experiments highlight the abnormal function of scaffolding proteins as a candidate mechanisms of post-traumatic stress disorder (PTSD), major depression, schizophrenia, and autism (Grant, 2012; Iasevoli, Tomasetti, & de Bartolomeis, 2013).

2. PSD-MAGUK family

PSD-MAGUKs, including PSD-95, SAP102, PSD-93, and SAP97, comprise five protein-protein interacting domains, namely three PDZ domains in the N-terminus, followed by a src homology-3 (SH3) domain and a guanylate kinase (GK) domain in the C-terminus (Xu, 2011). Through these domains, they interact with a variety of membrane proteins including NMDAR and kainate ionotropic glutamate receptors. The first and second PDZ (PDZ1/2) domains of PSD-95 bind to the extreme C-terminus of NMDAR subunits 2 (NR2) and regulate their localization, trafficking, and signaling.

2.1 PSD-95

PSD-95 is a core component of the PSD. Based on quantitative mass spectroscopy, PSD-95 is ~6-fold more abundant than PSD-93, ~8-fold more than SAP102, and ~40-fold more than SAP97 in PSDs of the adult rat forebrain (Nagura, Ishikawa, Kobayashi, Takao, Tanaka et al., 2012). PSD-95 organizes ionotropic GluRs and their associated signaling proteins to regulate the strength of synaptic activity.

In PSD-95 mutant mice, long-term potentiation (LTP) is greatly enhanced, whereas long-term depression (LTD) is absent (Migaud, Charlesworth, Dempster, Webster, Watabe et al., 1998), a finding confirmed with acute knockdown of PSD-95 (Ehrlich, Klein, Rumpel, & Malinow, 2007; Xu, Schluter, Steiner, Czervionke, Sabatini et al., 2008). Recently, a mutant cDNA knockin (KI) mice in which PDZ1/2 domains of PSD-95 are unable to bind ligands but retain their overall structure has been generated (Nagura et al., 2012). This approach was selected to assess the function of PSD-95 *in vivo* under conditions of minimized compensatory effects of other PSD-MAGUKs. Nevertheless, the KI mice showed decreased levels of mutant PSD-95, PSD-93, and AMPAR subunits, but increased levels of SAP102 in the PSD. Similar to conventional knockouts, these mice exhibited greatly enhanced hippocampal LTP.

The first behavioral characterization of mice lacking PSD-95 revealed a significant impairment of spatial memory (Migaud et al., 1998), an observation confirmed with data from KI mice (Nagura et al., 2012). Similarly, PSD knockouts exhibit robust impairment of conditioned taste aversion, however in appetitive conditioning with ethanol-induced place preference, these mice normally learn the ethanol-place contingency but develop place avoidance later on (Camp, Feyder, Ihne, Palachick, Hurd et al., 2011). In addition to appetitive learning, PSD-95 also interferes with the function of the reward system by affecting sensitization to psychostimulants. Regional downregulation of PSD-95 in the nucleus accumbens or caudate putamen augments the acute locomotor-stimulating effects of cocaine, though further behavioral changes in response to chronic cocaine are not found (Yao, Gainetdinov, Arbuckle, Sotnikova, Cyr et al., 2004).

Dysfunction of PSD-95 increases anxiety-like behavior and, interestingly, results in enhanced social interactions (Feyder, Karlsson, Mathur, Lyman, Bock et al., 2010). These and other findings presented in Table 1 show that the relationship between anxiety and social behavior is not always inversely correlated, and that, contrary to Shank scaffolds, MAGUK scaffolds most likely do not contribute to co-morbid anxiety and social deficits, as found in autism spectrum disorders.

Consistent with the memory deficits seen in mouse models, PSD-95 and SAP120 have been implicated in the progression of Alzheimer's disease based on a significant inverse correlation between their levels in the inferior temporal cortex and the severity of Alzheimer's disease symptoms (Proctor, Coulson, & Dodd, 2010). In contrast, PSD-95 levels in the frontal cortex of these patients is markedly increased (Leuba, Savioz, Vernay, Carnal, Kraftsik et al., 2008). Variation of the human DLG4 gene coding for PSD-95 has been linked to phenotypes relevant to autism spectrum disorders and Williams' syndrome (Feyder et al., 2010), whereas downregulation of PSD-95 and NMDAR NR2A and NR2B subunits in the prefrontal cortex was implicated in major depression (Feyissa, Chandran, Stockmeier, & Karolewicz, 2009). These findings urge for a better understanding of the composition and causal involvement of specific complexes MAGUKs in human disorders.

2.2 PSD-93

PSD-93, similar to PSD-95, binds to and clusters NMDAR subunits NR2A and NR2B at cellular membranes *in vitro*. PSD-95 and PSD-93 also show comparable expression profiles throughout development and contribution to basal transmission (Liaw, Zhu, Yaster, Johns, Gauda et al., 2008). Nevertheless, their effects on synaptic plasticity are dramatically different (Carlisle, Fink, Grant, & O'Dell, 2008): whereas PSD-95 knockout animals exhibit an enhancement of LTP and deficit in LTD, PSD-93 animals show a decrease of LTP in several paradigms. It is likely therefore that PSD-95 and PSD-93 form different protein complexes, and thereby influence the synaptic plasticity with different outcomes.

PSD-93 is highly abundant in the cerebellum, however mice lacking PSD-93 show normal sensory-motor development and do not display changes of motor behavior (McGee, Topinka, Hashimoto, Petralia, Kakizawa et al., 2001). In mice deficient in PSD-93, NMDAR-dependent morphine analgesic tolerance and morphine- withdrawal associated with abnormal sensitivity in response to mechanical, noxious thermal, and formalin-induced inflammatory stimuli. In addition, PSD-93 knockout mice display dramatic loss of jumping activity, a typical NMDAR-mediated morphine withdrawal abstinence behavior (Liaw et al., 2008). These findings can be attributed to reduced synaptic levels of NR2A and NR2B in dorsal horn and forebrain cortex neurons. The selective effect of PSD-93 deletion on synaptic NMDAR expression in these two major pain-related regions might be a promising new strategy for the prevention and treatment of opioid tolerance and physical dependence (Liaw et al., 2008).

2.3 SAP97

Unlike PSD-95, which interacts with AMPARs through direct binding to the transmembrane AMPAR regulatory proteins (TARPs), SAP97 binds directly the AMPAR subunit GluR1 (von Ossowski, Oksanen, von Ossowski, Cai, Sundberg et al., 2006). Studies on basal transmission showed that overexpression of SAP97 has little effect on synaptic AMPAR and NMDAR current, while others have shown a slight increase in both. When expressed in the absence of endogenous PSD-95 and PSD-93, however, SAP97 rescues the decrease of AMPAR currents (Howard, Elias, Elias, Swat, & Nicoll, 2010). Interestingly, this rescue depends on NMDAR and CaMK activity, suggesting the involvement of SAP97 in the LTP signaling pathway (Schluter, Xu, & Malenka, 2006). Accordingly, acute knockdown of SAP97 causes deficit in LTP (Nakagawa, Futai, Lashuel, Lo, Okamoto et al., 2004), however, when tested in knockout mice, LTP is normal (Howard et al., 2010). This apparent controversy suggests that SAP97 either plays a regulatory role in LTP without being an essential component of the LTP pathway, or that other proteins might have compensated for the loss of SAP97 in LTP. Evidence for a role of SAP97 in behavior is still lacking.

2.4 SAP102

SAP102 and PSD-95 bind to NMDA receptors through PDZ domains and cluster them at excitatory postsynaptic sites. SAP102 preferentially interacts with NR2A containing, whereas PSD-95 preferentially interacts with NR2B containing NMDAR (Xu, Xu, Deng, Liu, Yang et al., 2012). Ligand-binding deficient mutant SAP102 showed more efficient synaptic localization than wild-type SAP102, and when co-expressed with either the NR2A or NR2B, both subunits show decreased synaptic clustering even though the mutants are efficiently targeted to the synapse. This finding suggests that the PDZ domains of SAP102 are critical for the synaptic clustering of NMDAR but not SAP102 (Minatohara, Ichikawa, Seki, Fujiyoshi, & Doi, 2013).

Lack of SAP102 has no effect on basal transmission and presynaptic function, but causes the enhancement of high frequency induced LTP and spike timing dependent LTP. This phenotype is similar to that of PSD-95 mutant mice. However, in SAP102 null mice, inhibiting the ERK signaling pathway blocks LTP, whereas LTP in PSD-95 mutant mice is ERK-independent (Cuthbert, Stanford, Coba, Ainge, Fink et al., 2007).

To date, the only reported role of SAP102 in behavior is in studies with learning and memory. Mice lacking SAP102 exhibit impairments of spatial learning that can be reversed by extended training, and display different learning strategy from their wild type littermates (Cuthbert et al., 2007).

SAP102 is the first mental retardation-related protein directly linked to glutamate receptor signaling and trafficking, and increasingly recognized as a central mechanism in the regulation of synaptic formation and plasticity in the brain during cognitive development. Truncated mutations in the human disc-large homolog 3 (DLG3) coding SAP102 was found in 4 of 329 families with moderate to severe X-linked mental retardation (Tarpey, Parnau, Blow, Woffendin, Bignell et al., 2004). A novel splice site mutation (IVS6-1G > A) in the DLG3 gene, encoding the SAP102 in one out of 300 families with moderate to severe non-syndromic mental retardation, was also identified (Zanni, van Esch, Bensalem, Saillour, Poirier et al., 2010).

2.5 SAP90/PSD95 associated Protein3 (SAPAP3 or DLGAP3)

SAP90/PSD95-associated protein 3 (SAPAP3; also known as DLGAP3) is a postsynaptic scaffolding protein at excitatory synapses highly expressed in the striatum. Deletion of Sapap3 results in increased anxiety and compulsive grooming behavior leading to facial hair

loss and skin lesions that are alleviated by a selective serotonin reuptake inhibitor (Welch, Lu, Rodriguiz, Trotta, Peca et al., 2007). Electrophysiological, structural and biochemical studies of Sapap3-mutant mice reveal defects in cortico-striatal (Welch et al., 2007) but not thalamo-striatal synapses (Wan, Ade, Caffall, Ilcim Ozlu, Eroglu et al., 2013). These abnormalities are highly specific and can be notably rescued by lentiviral expression of Sapap3 in the striatum (Wan et al., 2013).

These findings demonstrate a critical link between abnormal SAPAP3 function at cortico-striatal synapses and obsessive-cognitive disorder (OCD)-like behaviors and strongly implicate SAPAP3 in the pathophysiology of human OCD.

2. Shank family

Shank proteins, encoded by the *Shank1*, *Shank2*, and *Shank3* genes, form the postsynaptic platform in PSD that brings together NMDA, AMPA, and mGlu receptor complexes. Shanks play a critical role in integrating the various postsynaptic membrane proteins, cell-adhesion molecules, signal components, other scaffolding proteins, and actin-based cytoskeleton of the PSD protein network (Gong & Lippa, 2010). Genetic manipulations of Shank proteins most prominently affect anxiety-like behavior but to a lesser extent cognitive behavior, at least when compared to MAGUK. There are notable differences, however, among different family members.

2.1 Shank1

Shank1 deficiency results in changes of the PSD composition, most notably decreased Homer 1b/c levels, and reduction of dendritic spines, yet LTP remains normal. Behaviorally the mice show impaired contextual fear conditioning and increased anxiety. Interestingly, spatial learning is improved but long-term spatial memory is profoundly impaired (Hung, Futai, Sala, Valtschanoff, Ryu et al., 2008). This result rules out that reduced motor function, another behavioral phenotype linked to Shank1 deficiency (Silverman, Turner, Barkan, Tolu, Saxena et al., 2011), confounds the observed cognitive deficits.

2.2 Shank2

Shank2 mice carrying a mutation identical to the ASD-associated microdeletion in the human *Shank* gene exhibit ASD-like behaviors including reduced social interaction, reduced social communication by ultrasonic vocalizations, and repetitive jumping. These mice show a marked decrease in NMDAR function. Knockouts of Shank2 exhibit several robust phenotypes, such as hyperactivity, anxiety, stereotypic behavior, and impaired social interactions (Schmeisser, Ey, Wegener, Bockmann, Stempel et al., 2012; Won, Lee, Gee, Mah, Kim et al., 2012). Notably, the social interaction deficits could be normalized by activating NMDAR or mGluR5 (Won et al., 2012). The cognitive phenotype of Shank2 mutants is less robust, as revealed by impaired spatial learning but normal object recognition.

2.3 Shank3

RNAi-knockdown of Shank 3, results in reduced mGluR5-dependent LTD, and decreased agonist-dependent pERK/CREB signaling. Allosteric activators of mGluR normalize the functional correlates of mGluR, suggesting that pharmacological enhancement of mGluR5 activity may rescue some phenotypes of Shank3 mutations (Verpelli, Dvoretzskova, Vicidomini, Rossi, Chiappalone et al., 2011).

Shank3 knockouts exhibit enhanced anxiety-like behavior, excessive self-grooming, and profoundly impaired social interactions. These behavioral effects were accompanied by

decreased spine density and NMDAR function in the cortico-striatal pathway, similar to the phenotype of SAPAP3 knockouts (Peca, Feliciano, Ting, Wang, Wells et al., 2011).

Mice carrying a mutation in the ankyrin repeat domain of Shank3 showed reduced glutamatergic transmission and LTP in the hippocampus with more severe deficits detected in the homozygous mice (Yang, Bozdagi, Scattoni, Wöhr, Roullet et al., 2012). Three independent cohorts were evaluated for magnitude and replicability of behavioral phenotypes relevant to autism and Phelan-McDermid syndrome. Mild social impairments were detected, primarily in juveniles during reciprocal interactions, while all genotypes displayed normal adult sociability on the three-chambered task. Impaired novel object recognition and rotarod performance were consistent across cohorts of null mutants (Yang et al., 2012). Repetitive self-grooming, reduced ultrasonic vocalizations, and deficits in reversal of water maze learning were detected only in some cohorts suggesting that discrete domains within the Shank3 gene determine the severity of symptoms.

Deficits of ProSAP/Shank signaling are thought to underlie several neuropsychiatric disorders, such as autism, schizophrenia, and Alzheimer's disease (Grabrucker, Schmeisser, Schoen, & Boeckers, 2011). A promoter variant of Shank1 has been linked to auditory working memory in patients with schizophrenia and in subjects clinically at risk for psychosis (Lennertz et al., 2012). On the other hand, mutations in the human Shank2 gene have been associated with ASD and intellectual disability (Berkel, Marshall, Weiss, Howe, Roeth et al., 2010). Similarly, mutations of the synaptic scaffolding protein gene Shank3 are strongly implicated in autism (Moessner, Marshall, Sutcliffe, Skaug, Pinto et al., 2007) and Phelan-McDermid 22q13 deletion syndrome (Bonaglia, Giorda, Mani, Aceti, Anderlid et al., 2006). Finally, Shank levels markedly change in the PSD of the brain of Alzheimer's disease patients. Namely, Shank 2 and Shank3 levels significantly increase and decrease, respectively (Gong, Lippa, Zhu, Lin, & Rosso, 2009), implicating disruption of glutamate receptor organization and function, which are normally controlled at Shank postsynaptic platforms in the PSD (Gong & Lippa, 2010; Iasevoli, Tomasetti, & de Bartolomeis, 2013).

3. Homer family

The most-studied mGluR-scaffold interactions are those with Homer family of proteins via the proline rich PPXFR domain. Homer proteins are encoded by three genes, *Homer 1*, *Homer 2*, and *Homer 3*, each with several splice variants including the long isoforms Homer1b/c and Homer2 and Homer 3 and short isoforms Homer1a and Ania3. Long homer isoforms were also identified as PSD proteins cupidin (Homer2) and PSD-Zip45 (Homer 1c) (Shiraishi-Yamaguchi & Furuichi, 2007). Homer proteins are characterized by a conserved Ena/VASP1 (EVH1) domain and long isoforms also have a coiled-coiled carboxy-terminal domain that mediates interactions with other proteins.

The long Homer scaffolds including Homer1b/c and Homer2 are predominantly found in the PSD where they directly associate with type I mGluRs, IP3Rs and Ryanodine receptors as well as various kinases including ERK and PI3K. Homer scaffolds also bind Shank, and thus indirectly links mGlu and NMDA receptors. In contrast, Homer1a (Ves1) is a short splice variant that lacks the coiled-coiled region, and acts as a dominant negative regulator of the function of long Homer proteins (Ango, Prezeau, Muller, Tu, Xiao et al., 2001). Homer proteins exhibit diverse regulatory roles in behavior, but appear to most notably affect addiction and sensitization to psychostimulant drugs.

3.1 Homer1

The interaction of type I mGluRs and Homer1 affects signaling, plasticity, and behavior in a number of different ways. Homer controls the trafficking of mGluR (Roche, Tu, Petralia,

Xiao, Wenthold et al., 1999), as well as mGluR-dependent signaling *via* ERK (Mao, Yang, Tang, Samdani, Zhang et al., 2005) and AKT/mTOR signaling (Ronesi & Huber, 2008). These signaling mechanisms are necessary for mGluR5-dependent LTD and LTP (Gerstein, O'Riordan, Osting, Schwarz, & Burger, 2012). The roles of mGluR/Homer complexes in plasticity, are reflected in memory processes. Homer1a specific knockouts have impaired fear memory formation (Inoue, Nakao, Migishima, Hino, Matsui et al., 2009). In the other hand, stress-induced interactions between Homer1a and mGluR5 enhance context fear conditioning (Tronson, Guzman, Guedea, Huh, Gao et al., 2010). Other proteins may mediate switching between mGluR and long versus short homer isoforms. For example, mice lacking Fmr1 protein exhibit less association of mGluR and Homer scaffolds (Ronesi & Huber, 2008), possibly due to increased association with Homer1a (Ronesi, Collins, Hays, Tsai, Guo et al., 2012).

Homer1 has been extensively studied for its role in addiction. Initial findings show a reduction of Homer1b/c scaffold after chronic cocaine administration and withdrawal, corresponding to reduced mGluR activity and increased sensitization (Kalivas, McFarland, Bowers, Szumlinski, Xi et al., 2003; Swanson, Baker, Carson, Worley, & Kalivas, 2001). Subsequent work has corroborated this finding showing that reductions in Homer1 are required for expression but not development of cocaine sensitization (Ghasemzadeh, Permenter, Lake, Worley, & Kalivas, 2003). In contrast to long homer isoforms, the role of Homer1a in development and maintenance of addiction remains unknown despite observations of increased Homer1a levels as a consequence of acute and chronic cocaine exposure (Ghasemzadeh, Windham, Lake, Acker, & Kalivas, 2009; Szumlinski, Abernathy, Oleson, Klugmann, Lominac et al., 2006).

Along with neuroplasticity, memory, and addiction, Homer1 is implicated in number of additional mood and executive functions. Homer1 knockout mice exhibit increased anxiety and depression-like behavior as well as impaired working memory and sensory gating (Szumlinski, Lominac, Kleschen, Oleson, Dehoff et al., 2005); but see (Jaubert, Golub, Lo, Germann, Dehoff et al., 2007). Subtle and specific deficits in social behaviors consist of increased social interactions, but decreased social transmission of food preference (Jaubert et al., 2007). The latter, however, may be more closely related to deficits in memory caused by Homer1 knockouts.

It is worth noting that the results from Homer1 knockouts should be interpreted with caution. First, knockout of Homer1 abolishes both the long and short forms of Homer1 known to oppose each other's function. Second, there is compensatory upregulation of Homer2 and Homer3 suggesting that the behavioral effects could be due to lack of Homer1 or increased interactions with other Homers. Third, Homer1 heterozygous mice, rather than showing a linear dose-dependent effect, in many cases exhibit behavioral changes in the opposite direction to those exhibited by Homer1 knockout mice (Jaubert et al., 2007). Finally, Homer 1 KO mice show a variety of general deficits, including impaired locomotor activity, motor learning, and low body weight that may confound interpretation in some paradigms.

3.2 Homer2

Like Homer1, Homer2 has been a focus of studies on addiction. Unlike Homer1, it seems that increases and decreases of Homer2 mediate responses to ethanol and cocaine, respectively. Homer2 KO mice show increased sensitization to cocaine, but increased sensitivity to the aversive and sedative effects of ethanol (Szumlinski, Dehoff, Kang, Frys, Lominac et al., 2004). In contrast, Homer2 overexpression causes increased behavioral sensitization and rewarding effects of ethanol (Szumlinski, Ary, & Lominac, 2008). Homer2, unlike Homer1, appears thus far to play a specific role in responding to ethanol and

cocaine, as well as locomotor sensitization to other drugs of abuse, including PCP (Szumlinski et al., 2004), but has no effect on sensorimotor gating, learning, long-term memory, working memory, or mood.

3.3 Homer3

Unlike Homer1 and Homer2, deletion of Homer3 does not cause sensitization of behavioral responding to cocaine, suggesting that despite similarities in binding to mGluRs, Homer3 has distinct though yet unknown functional consequences (Szumlinski et al., 2004). Homer3 interacts with type I mGluRs and those interactions are modified by cellular activity and CaMKII (Mizutani, Kuroda, Futatsugi, Furuichi, & Mikoshiba, 2008), suggesting a possible role in learning and memory.

Alterations of Homer1 expression and function have been linked to several different disorders. Concordant with rodent data, polymorphisms of Homer1 gene are associated with cocaine dependence in some populations (Dahl, Kampman, Oslin, Weller, Lohoff et al., 2005), and in human heroin and cocaine abusers, homer1b/c expression was increased in the amygdala (Okvist, Fagergren, Whittard, Garcia-Osta, Drakenberg et al., 2011). Two different polymorphisms of Homer1 have been linked to child-onset psychiatric disorders and suicidality (Strauss, McGregor, Freeman, Tiwari, George et al., 2012). Finally, schizophrenia has been associated with a single nucleotide polymorphism of Homer1 (Norton, Williams, Williams, Spurlock, Zammit et al., 2003) and Homer2 (Gilks, Allott, Donohoe, Cummings, Gill et al., 2010). This relatively broad array of disorders associated with homer polymorphisms is consistent with the many behavioral and affective alterations observed in animals with hetero- or homozygous knockout of Homer.

4. Other PSD scaffolds

4.1 Traf2 and NcK interacting kinase (TNIK)

TNIK is specifically expressed in neurons and highly enriched in the PSD and link synaptic protein complexes to the NMDAR via AKAP9 (Coba, Komiyama, Nithianantharajah, Kopanitsa, Indersmitten et al., 2012). It contains both serine-threonine kinase and scaffold domains and has been implicated in cell proliferation and glutamate receptor regulation *in vitro*. The disrupted in schizophrenia 1 (DISC1)-TNIK interaction regulates synaptic composition and activity by stabilizing the levels of key postsynaptic density proteins (Wang, Charych, Pulito, Lee, Graziane et al., 2011). NMDAR and mGluR regulate TNIK phosphorylation required for AMPA expression and synaptic function (Coba et al., 2012). Decreases in TNIK activity result in specific degradation of key postsynaptic molecules and changes in neuronal activity (Wang et al., 2011). Extensive characterization of TNIK-deficient mice reveals impaired neurogenesis in the dentate gyrus accompanied by deficits in pattern separation on a test of spatial discrimination. Object-location paired associative learning, which is dependent on glutamatergic signaling, is also attenuated. Finally, TNIK knockout mice display hyperlocomotor behavior that is rapidly reversed by GSK3 inhibitors, indicating the potential for pharmacological rescue of this behavioral phenotype (Coba et al., 2012). These data establish TNIK as a critical regulator of cognitive functions.

The function of TNIK in the brain is poorly understood, but its potential importance in psychiatry has been highlighted by several independent studies implicating TNIK in either schizophrenia or bipolar disorder (Glatt, Everall, Kremen, Corbeil, Sasik et al., 2005; Matigian, Windus, Smith, Filippich, Pantelis et al., 2007; Potkin, Turner, Guffanti, Lakatos, Fallon et al., 2009; Shi, Levinson, Duan, Sanders, Zheng et al., 2009). Whether this relates to the cognitive, emotional, or social aspects of these disorders remains to be established.

4.2 Kalirin/Kalirin-7

Kalirin is a family of proteins that is widely distributed in the CNS. Kalirin-7, the most abundant member, is prominently localized at the PSD of excitatory dendritic spines and significantly contributes to the regulation of spine morphology (Penzes, Johnson, Sattler, Zhang, Hugarir et al., 2001; Xie, Srivastava, Photowala, Kai, Cahill et al., 2007). Kalirin-7 directly interacts with the NR2B subunit of NMDA receptors (Kiraly, Lemtiri-Chlieh, Levine, Mains, & Eipper, 2011), thereby controlling synaptic localization of NR2B subunits and NMDA receptor synaptic functioning. Interestingly, while knockout of Kalirin-7 profoundly impairs LTP (Lemtiri-Chlieh, Zhao, Kiraly, Eipper, Mains et al., 2011), the effect of total Kalirin knockout is much smaller. Nevertheless, kalirin knockout results in profound impairments of working memory and aversive conditioning (Cahill, Xie, Day, Photowala, Barbolina et al., 2009; Xie, Cahill, Radulovic, Wang, Campbell et al., 2011). Selective Kalirin-7 deficiency impairs place preference for cocaine, reduces anxiety, and impairs passive avoidance (Ma, Kiraly, Gaier, Wang, Kim et al., 2008), which are mimicked in wild-type mice by administration of ifenprodil, a NR2B subunit selective antagonist (Kiraly et al., 2011). Locomotor activity, spatial learning and novel object recognition are not affected, suggesting that Kalirin-7 might predominantly regulate emotional and motivational behavior.

It is interesting that Kalirin-7 ablation in female and male mice exerts different behavioral effects in models of cocaine sensitization. The latter response is significantly enhanced in Kalirin-7-deficient males whereas females appear unaffected (Mazzone, Larese, Kiraly, Eipper, & Mains, 2012).

Based on significant changes of the levels of various Kalirin proteins, this family of scaffolds has been implicated in a number of synaptopathies encompassing Huntington's and Alzheimer's disease, schizophrenia, depression, and addiction (Mandela & Ma, 2012; Penzes & Remmers, 2012). Integrating gender differences in these studies may help to identify further specificity of the behavioral roles of Kalirin.

4.3. IQGAP1

IQGAP1 belongs to the IQGAP family of molecular scaffolds named for their homology to GTPase-activating proteins (GAPs) and isoleucine/glutamine (IQ) (calmodulin-binding) motifs. Three isoforms, IQGAP1, IQGAP2, and IQGAP3, that mediate a variety of biological functions, have been described in mammals (White, Erdemir, & Sacks, 2012). In the brain, IQGAP1 and IQGAP3 regulate dendritic spine morphology (Gao, Frausto, Guedea, Tronson, Jovasevic et al., 2011; Swiech, Blazejczyk, Urbanska, Pietruszka, Dortland et al., 2011) and neurite outgrowth (Wang et al., 2011), respectively. We recently found, using IQGAP1 KO mice, that this scaffold plays an important role in ERK-dependent signal transduction, NR2A trafficking, and behavior (Gao et al., 2011). Mice lacking IQGAP1 exhibit significant impairments in memory formation but intact sensory-motor development, locomotor activity, anxiety- and depression-like behavior. These findings unravel important roles of IQGAP1 and suggest a specific involvement of the NR2A/IQGAP1/ERK signaling module in cognitive versus emotional and motivational behavior.

IQGAP1 serves as a scaffold for several signaling pathways, such as Lis1, Cdc42, B-Raf, and ERK, which regulate spine density (Ide & Lewis, 2010; Kholmanskikh, Koeller, Wynshaw-Boris, Gomez, Letourneau et al., 2006; Reiner, Sapoznik, & Sapir, 2006; Ryu, Futai, Feliu, Weinberg, & Sheng, 2008; Yuan, Zhou, Wang, Li, Li et al., 2010) and show marked abnormalities in schizophrenia (Rastogi, Zai, Likhodi, Kennedy, & Wong, 2009) and other psychiatric illnesses. Analyses of IQGAP family polymorphisms and gene

expression patterns may reveal significant contribution to cognitive physiology and pathology in humans.

4.4 SynGAP1

SynGAP1 is a GTPase-activating protein for H-Ras that colocalizes with NMDA receptors at excitatory synapses through direct interactions with the PDZ domains of PSD-95 (Chen, Rojas-Soto, Oguni, & Kennedy, 1998; Kim, Liao, Lau, & Huganir, 1998). Together with CaMKII, SynGAP1 is the most abundant PSD protein, both contributing about 8% of the total protein content (Cheng, Hoogenraad, Rush, Ramm, Schlager et al., 2006). SynGAP1 is largely localized to dendritic spines in neocortical pyramidal neurons (Chen, Rojas-Soto, Oguni, & Kennedy, 1998; Kim, Liao, Lau, & Huganir, 1998) where it suppresses signaling pathways linked to NMDAR-mediated synaptic plasticity and membrane insertion of AMPAR (Kim et al., 2005; Krapivinsky et al., 2004). The homozygous SynGAP1 knockout is lethal, therefore most studies on this scaffold were carried out with mutants lacking only one allele of the gene. LTP is significantly impaired in mice with reduced SynGAP1 function but spatial learning is only modestly impaired (Komiyama, Watabe, Carlisle, Porter, Charlesworth et al., 2002). A comparative analysis between PSD-95 and SynGAP1 showed that, although PSD-95 couples SynGAP1 to NMDA receptors, PSD-95 and SynGAP mutant mice exhibit distinct physiological and behavioral phenotypes, possibly due to the coupling of PSD-95 to multiple downstream signaling pathways with different roles in LTP and learning (Komiyama et al., 2002). Additional phenotypes associated with reduced SynGAP1 levels include marked hyperactivity, impairments of sensory gating, aversive conditioning, social interactions, and working memory (Guo, Hamilton, Reish, Sweatt, Miller et al., 2009), whereas anxiety is reduced (Muhia, Yee, Feldon, Markopoulos, & Knuesel, 2010). Impaired extinction of appetitive conditioning (Muhia, Feldon, Knuesel, & Yee, 2009) and increased sensitivity to thermal pain (Duarte, Duan, Nicol, Vasko, & Hingtgen, 2011) are also observed.

Autosomal-dominant de novo mutations in *SynGAP1* that lead to truncation of the full-length protein are thought to cause sporadic intellectual disability in ~74% of cases (Hamdan, Daoud, Piton, Gauthier, Dobrzaniecka et al., 2011; Hamdan, Gauthier, Spiegelman, Noreau, Yang et al., 2009; Krepischi, Rosenberg, Costa, Crolla, Huang et al., 2010) with some patients also having an autism spectrum disorder (Hamdan et al., 2011). These mutations appear to be common and more prevalent than fragile X syndrome, underscoring a key role of *SynGAP1* in cognitive processes (Hamdan et al., 2011).

4.5 Vezatin

Vezatin is an integral membrane protein associated with cell-cell adhesion complex and actin cytoskeleton. It is expressed in the developing and mature mammalian brain, but its neuronal function is unknown. Vezatin localizes in spines in mature mouse hippocampal neurons and codistributes with PSD95. Vezatin knock-down in cultured hippocampal neurons and Vezatin conditional knockout in mice led to a significantly increased proportion of stubby spines and a reduced proportion of mature dendritic spines (Danglot, Freret, Le Roux, Narboux Neme, Burgo et al., 2012; Sanda, Ohara, Kamata, Hara, Tamaki et al., 2010). The reduced expression of Vezatin did not compromise the maintenance of synaptic connections thus leaving the amplitude and frequency of miniature EPSCs of hippocampal neurons intact. However, the AMPA/NMDA ratio of evoked EPSCs was reduced, suggesting impaired functional maturation of excitatory synapses (Danglot et al., 2012). Forebrain-specific conditional ablation of Vezatin induced anxiety-like behavior and impaired cued fear-conditioning without affecting spatial learning and locomotor activity (Danglot et al., 2012). Vezatin thus emerges as an important regulator of dendritic spine morphogenesis, functional synaptic maturation, and emotional behavior.

4.6 The insulin receptor substrate of 53 kDa (IRSp53)

IRSp53 is strongly enriched in the postsynaptic density of excitatory synapses where it links shank proteins to PSD-95 and via its PDZ-binding and SH3 domains, induces the formation of a triple complex (shank1/IRSp53/PSD-95) (Soltau, Berhorster, Kindler, Buck, Richter et al., 2004). Reduction of IRSp53 levels by RNAi reduces the density, length, and width of dendritic spines (Choi, Ko, Racz, Burette, Lee et al., 2005).

Mice lacking this scaffold show significantly enhanced LTP but impaired spatial learning, novel object recognition, and contextual fear conditioning (Kim, Choi, Yang, Chung, Kim et al., 2009; Sawallisch, Berhorster, Disanza, Mantoani, Kintscher et al., 2009), similar to PSD-95 knockouts.

IRSp53 is the key effector of Cdc42, whose decreased levels have been linked to the decreased density of dendritic spines in the dorsolateral prefrontal cortex of subjects with schizophrenia (Hill, Hashimoto, & Lewis, 2006; Ide & Lewis, 2010).

4.7 Norbin

Interaction of mGluR with scaffold proteins also mediates complex cognitive behavior (Wang, Nong, Bazan, Greengard, & Flajolet, 2010). Norbin, a neuronal specific protein, interacts with mGluR5, and mediates signaling via GRKs and arrestins. Knockouts of norbin result in deficits reminiscent of schizophrenia, including deficits in sensorimotor gating (prepulse inhibition) and locomotor alterations (Wang, Westin, Nong, Birnbaum, Bendor et al., 2009). The role of norbin in other mGluR5 mediated or modulated behaviors, including anxiety and memory formation, remains to be determined, and seems very likely given the prominent levels of norbin in regions including bed nucleus of stria terminalis and amygdala. This possibility is further supported by increased norbin expression in these regions after fear conditioning (Wang et al., 2010).

4.8 Densin-180

Densin-180 mediates mGluR5 function and membrane localization (Carlisle, Luong, Medina-Marino, Schenker, Khorosheva et al., 2011), possibly via interaction with Shank. Although it remains unknown whether densin-180 directly interacts with mGluR5, it is clear that knockout of densin-180 leads to deficits in mGluR membrane localization and mGluR-dependent LTD. Additionally, in knockouts of densin-180, mice exhibit less of the DISC1 scaffold at synapses, a protein that has been linked to models of schizophrenia and other disorders (Hayashi-Takagi, Takaki, Graziane, Seshadri, Murdoch et al., 2010). Importantly, DISC1 critically interacts with the scaffold Kalirin-7 (Hayashi-Takagi et al., 2010) thus Densin-180 may be another mechanism of molecular and functional connection between mGluR and NMDAR.

5. Summary and conclusion

The early recognition of the specificity of the behavioral actions of PSD scaffolds (Migaud et al., 1998) still holds true, even as more proteins are being identified and characterized, as shown in Table 1. Overall, the findings show a clear dissociation between synaptic plasticity (LTP and LTD) and memory, or other behaviors. While this is not entirely surprising, the findings are a reminder that explanations for the role of LTP in behavior need to be considered more systematically. For example, the alternative that LTP may serve as an arousal or attention device by which the brain nonspecifically changes the salience of external stimuli (Shors & Matzel, 1997) seems more consistent with the occurrence of various behavioral abnormalities accompanying LTP and LTD deficits. Another possibility is that different types of plasticity, such as formation of multi-innervated spines, enable

memory formation when LTP is absent (Nikonenko, Boda, Steen, Knott, Welker et al., 2008; Radwanska, Medvedev, Pereira, Engmann, Thiede et al., 2011). Changes of scaffold levels induce changes of many behaviors, nevertheless, it appears that MAGUK scaffolds most robustly affect memory, Shank affects anxiety and social interactions, and Homer modulates addiction. Kalirin-7 and SynGAP1 appeared to be the most pleiotropic, a somewhat paradoxical observation given that kalirin-7 knockouts have more profound effects than total kalirin knockouts and the fact that SynGAP1 mutant mice lack only one functional allele. It is possible, however, that partial genetic manipulations are less effective in triggering compensatory processes than complete gene deletion knockouts and thus result in stronger behavioral phenotypes. Interestingly, kalirin and SynGAP1 are also the only scaffolds implicated in anxiogenic-like behavior, whereas all other scaffolds appeared to be anxiolytic.

The discussed studies, based on manipulations of scaffold protein levels by engineered genetic manipulations, have significantly advanced our understanding of the behavioral roles of PSD scaffolds for glutamate receptors. Some of the models are specifically designed to mimic human genetic abnormalities whereas others can translate to a variety of real life situations triggering changes of scaffold levels and trafficking. For example, expression of PSD-95, GluR1, NR1 in PFC is decreased by early life stressors, which disrupt brain development and profoundly affect a wide-range of behaviors in adult animals (Hermes, Li, Duman, & Duman, 2011). Similarly, adult rats respond to chronic elevation of the stress hormone corticosterone show decreased PSD-95 (Cohen, Louneva, Han, Hodes, Wilson et al., 2011). Other stressful situations, such as cocaine withdrawal, selectively decrease Homer1b/c levels without alterations of PSD-95. With this in mind, it is important to emphasize that better understanding of the regulation of PSD scaffolds is required before causal links between their roles in translating specific experiences to corresponding behaviors can be made. An important consideration when interpreting findings of PSD scaffolds is that these molecules do not solely interact with glutamate receptors. For example, PSD-95 interaction with the serotonin receptors 5-HT(2A)- and 5-HT(2C) is important for sensory gating (Abbas, Yadav, Yao, Arbuckle, Grant et al., 2009), whereas interaction with the enzyme nitric oxide synthase contributes to neuronal plasticity (Radwanska et al., 2011). Nevertheless, if part of the same macromolecular complex, these receptors and enzymes are likely to function in concert with the glutamatergic system.

A notable gap in the field is the shortage of studies on PSD scaffolds in depression-like behavior. This is particularly surprising given the revived interest in the role of NMDAR and PSD-95 in major depression (Karolewicz, Szebeni, Gilmore, Maciag, Stockmeier et al., 2009; Pittenger, Sanacora, & Krystal, 2007), and will be likely subjected to systematic research in the future. Further dissection of the role of PSD scaffolds in mood regulation, anxiety, memory, social behavior, and sensory gating, will expand our understanding of the relationship between glutamate-regulated behaviors. Such knowledge has a significant translational potential for the development of novel treatment approaches for anxiety, depression, autism, schizophrenia, dementia, and addiction- particularly for targeting co-morbid conditions that are highly frequent in all of these disorders.

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- Glutamate receptor scaffolding proteins regulate complex behavior
- PSD-like, Kalirin, Shank, Homer, and other scaffolds distinctively contribute to memory, addiction, sensory gating, social interactions, anxiety, and pain
- Reduced expression and mutations of PSD scaffold genes are linked to psychiatric disorders

Figure 1.
Schematic representation of the PSD scaffolds and their interaction with NMDAR and mGluR discussed in this review.

Table 1

Behavioral effects of PSD scaffolds deduced from genetically engineered mouse models*

Plasticity					Behavior **												
Scaffold	LTP	LTD	Sensory motor	Locomotor	Sensory Gating	Spatial memory	NOR	AvC	ApC	Addic.	Sens.	Working memory	Anxiety	Depression	Social behavior		
PSD-95	-1-5	+1-5	+80.1	+5	+6	+1		+7	-7		-0 ²		-5.8		+0 ⁵ , -8		
PSD-93	+9		0 ¹⁰	0 ¹⁰						+11							
SAPAP3													-12,13				
SAP102	-14		0 ¹⁴			+14											
TNIK				-15		+15	+15										
Kalirin	+16			-16	+16	+16	0 ¹⁶	+17				+17	+17		+17		
Kalirin7	+18,19			0 ¹⁸		0 ¹⁸	0 ¹⁸	+18	+20				+18		+18		
IQGAP1	0 ²¹		0 ²¹	0 ²¹		+21	+21	+21					0 ²¹	0 ²¹			
SynGAP	+22			-23,25	-23	± 22,25	0 ²⁵	+23	-24			+23	+25		+23		
Vezatin				-26		0 ²⁶		+26					-26				
IRSp53	-27,28		0 ²⁸	0 ²⁸		+28	+28	+27					0 ²⁷				
Shank1	0 ²⁹		+29	+30		-29		+29					-29		0 ²⁹		
Shank2	+31,32		0 ³¹	0 ³¹		+32	0 ³¹					0 ³¹	-31,32		+31,32		
Shank3	+33	-33		0 ³⁴		0 ³⁵	0 ³⁵						-34		+34		
Homer1	+36	+37		-38	+39 0 ⁴⁰	+40			+38, 0 ³⁸	+38	-41	+39	-38	+38	-40		
Homer2				0 ³⁸	0 ³⁸				+42, 0 ⁴³	+42	-42, 42, 43	0 ³⁸	0 ³⁸	0 ³⁸			
Norbin	+44	+44			+44						-44						
Densin-180	+45	0 ⁴⁵	0 ⁴⁵	+45	+45		+45						-45		-45		
Tamalin									+46	+46							

*1 Migaud et al., 1998;

2 Yao et al., 2004;

- ³Xu et al., 2008;
- ⁴Ehrlich et al., 2007;
- ⁵Nagura et al., 2012;
- ⁶Abbas et al., 2009;
- ⁷Camp et al., 2011;
- ⁸Feyder et al.,2010;
- ⁹Carlisle et al., 2008;
- ¹⁰McGee et al., 2001;
- ¹¹Liaw et al., 2008;
- ¹²Welch et al., 2007;
- ¹³Wan et al., 2013;
- ¹⁴Cuthbert et al., 2007;
- ¹⁵Coba et al., 2012;
- ¹⁶Cahill et al., 2009;
- ¹⁷Xie et al., 2011;
- ¹⁸Ma et al., 2008;
- ¹⁹Lemtiri-Chlieh et al., 2011;
- ²⁰Kiraly, Eipper-Mains, Ma, & Eippe, 2011;
- ²¹; Gao et al., 2011;
- ²²Komiyama et al., 2002;
- ²³Guo et al., 2009;
- ²⁴Muhia et al., 2009;
- ²⁵Muhia et al., 2010;
- ²⁶Danglot et al., 2012;
- ²⁷Sawallich et al., 2009;

- ²⁸ Kim et al., 2009;
- ²⁹ Hung et al., 2008;
- ³⁰ Silverman et al., 2011;
- ³¹ Schmeisser et al., 2012;
- ³² Won et al., 2012;
- ³³ Verpelli et al., 2011;
- ³⁴ Peca et al., 2011;
- ³⁵ Yang et al., 2012;
- ³⁶ Gerstein et al., 2012;
- ³⁷ Ronesi & Huber 2008;
- ³⁸ Szumlinski et al., 2005;
- ³⁹ Kalivas et al., 2004;
- ⁴⁰ Jaubert et al., 2007;
- ⁴¹ Swanson et al., 2001;
- ⁴² Szumlinski et al., 2003;
- ⁴³ Szumlinski et al., 2008;
- ⁴⁴ Wang et al., 2009;
- ⁴⁵ Carlisle et al., 2011;
- ⁴⁶ Ogawa et al., 2007;

^{**} Effects: +, enhancement; −, attenuation; ∅, no effect.

Abbreviations: NOR, novel object recognition; AvC, aversive conditioning; ApC, appetitive conditioning; Addic., addiction; Sens., sensitization;