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PSD95: A synaptic protein implicated in schizophrenia or autism?

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ABSTRACT

The molecular components of the postsynaptic density (PSD) in excitatory synapses of the brain are currently being investigated as one of the major etiologies of neurodevelopmental disorders such as schizophrenia (SCZ) and autism. Postsynaptic density protein-95 (PSD-95) is a major regulator of synaptic maturation by interacting, stabilizing and trafficking *N*-methyl-D-aspartic acid receptors (NMDARs) and α-amino-3-hydroxy-5-methyl-4-isox-azoleproprionic acid receptors (AMPARs) to the postsynaptic membrane. Recently, there has been overwhelming evidence that associates PSD-95 disruption with cognitive and learning deficits observed in SCZ and autism. For instance, recent genomic and sequencing studies of psychiatric patients highlight the aberrations at the PSD of glutamatergic synapses that include PSD-95 dysfunction. In animal studies, PSD-95 deficiency shows alterations in NMDA and AMPA-receptor composition and function in specific brain regions that may contribute to phenotypes observed in neuropsychiatric pathologies. In this review, we describe the role of PSD-95 as an essential scaffolding protein during synaptogenesis and neurodevelopment. More specifically, we discuss its interactions with NMDA receptor subunits that potentially affect glutamate transmission, and the formation of silent synapses during critical time points of neurodevelopment. Furthermore, we describe how PSD-95 may alter dendritic spine morphologies, thus regulating synaptic function that influences behavioral phenotypes in SCZ versus autism. Understanding the role of PSD-95 in the neuropathologies of SCZ and autism will give an insight of the cellular and molecular attributes in the disorders, thus providing treatment options in patients affected.

1. Introduction

Synaptic dysregulation of dendritic spines during neurodevelopment is becoming increasingly linked to neurological diseases. Schizophrenia (SCZ) and autism are highly prevalent disorders characterized by synaptic abnormalities that lead to social impairments and cognitive deficits in individuals (Hutsler and Zhang, 2010; Selemon and Goldman-Rakic, 1999). The on-set and symptomology of these maladies are currently being explored at the dendritic spines to gain a better understanding of the effects and potential treatment options. SCZ is a heterogeneous mental health disorder that affects 1.1% of the human population. Typically, the on-set of SCZ occurs during the adolescent age range and consists of positive, negative and cognitive symptoms. Positive and negative symptoms involve hallucinations/delusions and emotional blunting, respectively. The cognitive dysfunctions include impaired working memory, lack of executive functions and attention deficits. In contrast, autism is a neurodevelopmental disorder that affects on average 1 in 68 of the childhood population and is considered within the autism spectrum disorder (ASD) (Toro et al., 2010). Autistic patients experience symptoms that include behavioral abnormalities such as repetition, reduced vocal communication, and aberrant social interactions. The prevailing theories of SCZ and autism etiologies suggest that a disruption of the synapse during neurodevelopment will cause impairments in synaptic plasticity and synaptic processing that are characteristic of these disorders.

The postsynaptic density (PSD) is a dense localized area within dendritic spines of excitatory synapses and is comprised of receptors, kinases, structural proteins and signaling molecules associated with synaptic plasticity. Perhaps the most abundant protein of the PSD is postsynaptic density protein-95 (PSD-95) (Cheng et al., 2006; Cho et al., 1992), a member of the membrane-associated guanylate kinase family (MAGUK), a scaffolding protein located at excitatory synapses and is involved in the stabilization, recruitment and trafficking of *N*-methyl-D-aspartic acid receptors (NMDARs) and α-amino-3-hydroxy-5-methyl-4-isox-azoleproprionic acid receptors (AMPARs) to the postsynaptic membrane (Chen et al., 2000; Kornau et al., 1995). PSD-95 is an essential component involved in glutamatergic transmission, synaptic plasticity, and dendritic spine morphogenesis during neurodevelopment (Funke et al., 2005; Gilman et al., 2011; Kim and Sheng, 2004). Therefore, it is plausible that PSD-95 dysfunction during development

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Table 1
Mutations identified in the *DLG4* gene in schizophrenia, autism and intellectual disability.

Mutation	Disorder	Methods	Reference
DLG4; Singleton	Schizophrenia	Exome sequence analysis	(Purcell et al., 2014)
DLG4; de novo copy number variation (CNV)	Autism	NETBAG analysis	(Gilman et al., 2011)
DLG4-G241S	Autism	Ion PGM platform sequencing	(Xing et al., 2016)
DLG4; de novo	Autism	smMIP screening	(Stessman et al., 2017)
DLG4; de novo	Intellectual disorder	Meta-analysis	(Lelieveld et al., 2016)

may alter synaptic plastic events at the dendritic spines that contribute to the malformations of the synapse-associated with neurological disorders.

There is overwhelming evidence from human and animal studies that suggest PSD-95 disruption is linked to the neuropathologies of SCZ and autism. Specifically, a variety of sequencing techniques and analytics were used to identify PSD-95 mutations in SCZ and autism patients (Table 1). For instance, exome sequencing studies of SCZ patients show disrupted mutations of proteins located in the excitatory synapses of the PSD such as NMDAR and PSD-95 (Fromer et al., 2014; Purcell et al., 2014). Further evidence reveals a significant decrease in PSD-95 mRNA and protein expression levels in the dorsolateral and dorsomedial prefrontal cortex of schizophrenic postmortem patients (Ohnuma et al., 2000; Catts et al., 2015), suggesting an association between PSD-95 dysfunction and SCZ. PSD-95 has also been shown to be involved in a network of interactions with high-risk ASD genes that include SHANK, HOMER, neuroligin, and FMR1 (De Rubeis et al., 2014; Gilman et al., 2011; Tsai et al., 2012). Additionally, in mouse studies, deletion of the *DLG4 gene* (encodes PSD-95) causes behavioral abnormalities such as an increase in repetitive behavior, decreased vocalization, and irregular social interactions consistent with phenotypes observed in ASD patients (Feyder et al., 2010). Furthermore, in a recent genetic study, *DLG4* was identified as a candidate gene disrupted in intellectual disability (ID) (Lelieveld et al., 2016) (Table 1), a cognitive and mental disorder characterized by a reduction of dendritic spines. Interestingly, PSD-95 has direct interactions with ID-related proteins within the excitatory PSD that include Arc and Interleukin-1-receptor accessory protein-like 1 (IL1RAPL1), responsible for regulating spine density and function (Fernández et al., 2017; Pavlowsky et al., 2010; Valnegri et al., 2011). Therefore, PSD-95 deficiencies could attribute to the loss of spines and cognitive impairments associated with the ID. In this review, we provide an in-depth discussion of the role of PSD-95 in glutamatergic transmission and speculate on its implications in SCZ and autism. Moreover, we outline evidence that illustrates the effects of PSD-95 dysfunction and NMDAR regulation that include the formation of silent synapses. Lastly, we propose potential treatment options that restore PSD-95 within dendritic spines as a therapeutic option for SCZ and autism.

2. PSD-95: a major component of the neurodevelopment of excitatory synapses

PSD-95 (also known as SAP90, synapse-associated protein 90) is encoded by the *DLG4* (discs large homolog 4) gene in humans and is a major member of the MAGUK family. It functions as a scaffolding protein at excitatory synapses of the PSD. PSD-95 consists of three N-terminal PDZ domains (PSD-95, dlg, and zonula occludens-1), src homology domain (SH3), and a catalytically inactive guanylate cyclase domain (GUK) (Cho et al., 1992; Kim and Sheng, 2004). PSD-95 binds via PDZ domains directly to carboxy-terminal tails of NMDA receptor subunits, NR2A and NR2B, and to the AMPA receptor accessory proteins through stargazin/TARPs (Zhang et al., 2013) (Fig. 1). Moreover, PSD-95 is a major component of a large network of proteins within PSD including ion channels, receptors, adhesion proteins, scaffolding proteins, and signaling molecules that influence glutamatergic transmission. For instance, PSD-95 has direct interactions with K^+ channels, neuroligin, and nNOS; and indirect interactions with mGluR1/5 via GKAP (Brenman et al., 1996; Irie et al., 1997; Kim et al., 1997; Kim and Niethammer, 1995) (Table 2). Additional members of the MAGUK family include SAP102, SAP97, and PSD-93: and are also responsible for the recruitment and stabilization of NMDA and AMPA receptors.

PSD-95 has long been associated with synaptic plasticity of glutamatergic synapses during neurodevelopment due to its interaction and functional implications of NMDA and AMPA receptors. Synaptic plastic processes such as long-term potentiation (LTP) and long-term depression (LTD) are heavily involved in synaptic maturation of the dendritic spine; therefore, alterations of the PSD may compromise the integral process of spine formation leading to neuropathologies of the synapse. Thus, PSD-95 may act as a key component involved in regulating synaptic strength by controlling spine formation and/or spine elimination/pruning.

3. PSD-95 mediates NMDA receptor clustering and function

The PSD site for excitatory glutamatergic transmission is mainly composed of glutamatergic receptors, including both NMDA and AMPA receptors. NMDA receptors are essential for synaptic plasticity and cortical development, and functional processes such as learning and working memory (Collingridge et al., 2013; Dumas, 2005). NMDA receptors consist of a hetero-tetrameric complex that contains an obligatory homodimer of NR1 and homodimers or heterodimers of either NR2A-D or NR3A-D subunits. NR2-containing subunits are involved in mediating calcium (Ca^+) influx at the postsynaptic membrane; however, the open probability and duration of Ca^+ flux are subunit specific. For instance, NR2B-containing NMDA receptors have slower kinetics and a slower decay time compared to NR2A-containing NMDA receptors, thus resulting in a larger flow of Ca^+ within the synapse. PSD-95 influences NMDA receptor transmission via direct interaction and stabilization of specific NR2-containing NMDA receptors to the postsynaptic membrane. PSD-95 RNAi knockdown increases NR2B clustering at the postsynaptic synapse in cultured hippocampal neurons (Bustos et al., 2014). Additionally, in the hippocampus of a PSD-95 knockout mouse model, a reported increase in NMDAR decay was shown, suggesting a high presence of NR2B-containing NMDA receptors, thus corroborating previous findings (Beique et al., 2006). NR2B is essential for synaptic maturation during development (Monaco and Gulchina, 2015) and cognitive processes within the adult (Wang et al., 2013). However, an overabundance may be hazardous due to the significant increase in Ca^+ conductance that could lead to excitotoxicity and neuronal death (Hardingham, 2006; Monaco and Gulchina, 2015). Therefore, a downregulation of PSD-95 may subsequently result in a substantial increase in Ca^+ influx. Ca^+ excitotoxicity within specific areas may impair tissue function, leading to neuropathologies depending on the brain region.

4. PSD-95: a regulator of NMDA receptor development

Glutamatergic receptor composition varies at the PSD of excitatory synapses during neurodevelopment. For instance, PSD scaffolding