Neurobiology of Learning and Memory 105 (2013) 3–12

Contents lists available at SciVerse ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Modulation of behavior by scaffolding proteins of the post-synaptic density

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ARTICLE INFO

Article history:
Available online 20 May 2013

Keywords:
Glutamate receptor
Scaffold
Behavior
Psychiatric disorders

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.

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, 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 (Fig. 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

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http://dx.doi.org/10.1016/j.nlm.2013.04.014

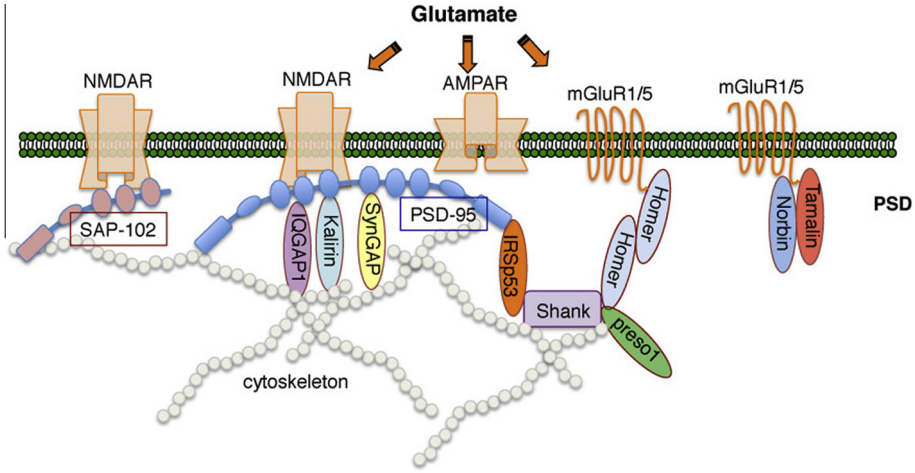

Fig. 1. Schematic representation of the PSD scaffolds and their interaction with NMDAR and mGluR discussed in this review.

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 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 et al., 1998), a finding confirmed with acute knockdown of PSD-95 (Ehrlich, Klein, Rumpel, & Malinow, 2007; Xu 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

Table 1
Behavioral effects of PSD scaffolds deduced from genetically engineered mouse models.[a]

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

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

[a] [1]Migaud et al. (1998); [2]Yao et al. (2004); [3]Xu et al. (2008); [4]Ehrlich et al. (2007); [5]Nagura et al. (2012); [6]Abbas et al. (2009); [7]Camp et al. (2011); [8]Feyder et al. (2010); [9]Carlisle, Fink, Grant, and O'Dell (2008); [10]McGee et al. (2001); [11]Liaw et al. (2008); [12]Welch et al. (2007); [13]Wan et al. (2013); [14]Cuthbert et al. (2007); [15]Coba et al. (2012); [16]Cahill et al. (2009); [17]Xie et al. (2011); [18]Ma et al. (2008); [19]Lemtiri-Chlieh et al. (2011); [20]Mains, Kiraly, Eipper-Mains, Ma, and Eippe (2011); [21]Gao et al. (2011); [22]Komiyama et al. (2002); [23]Guo et al. (2009); [24]Muhia et al. (2009); [25]Muhia et al. (2010); [26]Danglot et al. (2012); [27]Sawallich 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, O'Riordan, Osting, Schwarz, and Burger (2012); [37]Ronesi and 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).

[b] Effects: +, enhancement; −, attenuation; ø, no effect.