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Emerging Roles of Dlg-Like PDZ Proteins in the Organization of the NMDA-Type Glutamatergic Synapse[1]

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A group of proteins found at cell-cell junctions have a common structural domain, called PDZ—a stretch of 80-90 amino acid residues initially identified in the three proteins PSD-95, Dlg, and ZO-1. This domain is found in various proteins from bacteria to mammals and is involved in protein-protein interaction. Recently, many proteins containing this domain were identified in the nervous system by molecular cloning and shown to interact with other synaptic proteins, including various transmitter receptors, ion channels, and signal transducers. These PDZ-containing proteins are mostly located near the synaptic membrane and are, therefore, speculated to transport associated proteins to the synapse and/or anchor them at the synaptic sites. Alternatively, as a single molecule often contains multiple PDZ domains that can interact with each other, it may cluster all these synaptic molecules and facilitate their signaling at synaptic sites. This review focuses on the best characterized PDZ-containing proteins that interact with *N*-methyl-D-aspartate (NMDA)-type glutamate receptors and discusses their functions in synaptic organization.

Key words: guanylate kinase, NMDA receptor, palmitoylation, postsynaptic density, receptor clustering.

Neurotransmitter receptors and intracellular signal-transducers are essential molecular machinery for neurotransmission and synaptic plasticity. Unless properly arranged both spatially and temporally, however, the postsynaptic machinery cannot work effectively. At the neuromuscular synapse, for instance, various signal-transducing molecules and cytoskeletal proteins are associated with nicotinic acetylcholine receptors and regulate their spatial compartmentalization and cytoskeletal interactions, both of which are suggested to influence synaptic efficacy (*1*). Thus, functional impairment of these receptor-associated molecules results in abnormal neurotransmission to the muscle. These observations on neuromuscular synapses suggest that mechanisms controlling subcellular distributions of such principal players in the synapse may form a basis for synaptic plasticity. In line with this, recent interest in neuroscience research has focused on the mechanisms underlying the subcellular compartmentalization of receptors for glutamate, the most prevalent excitatory neurotransmitter in mammalian brain.

Many proteins that share a common motif, called the PDZ domain, are located at cell-cell junctions; for neurons, it is the synaptic junction. The PDZ domain refers to a stretch of 80-90 amino acid residues that was initially identified in the three proteins, PSD-95, Dlg, and ZO-1 (*2-4*). This domain is conserved among various proteins from bacteria to mammals and mediates protein-protein interactions through its high affinity binding to C-terminal residues of target proteins (*5-7*). More than 50 different proteins in mammals have, so far, been shown to contain PDZ domain(s) and are classified into the following groups based on their structural homology; membrane-associated guanylate kinases (MAGUK) (including p55-like proteins, tight junction proteins, and Dlg-like proteins), syntrophins, tyrosine phosphatases, dsh homologues, and LIM domain proteins (*6*).

Those proteins in the Dlg family that interact with *N*-methyl-D-aspartate (NMDA)-type glutamate receptors are the focus of this review. The NMDA receptor channel is one of the ionotropic glutamate receptors and is assembled from the NR1 subunit and any of four NR2 subunits (NR2A, NR2B, NR2C, and NR2D). Crucial functions in synaptic development and plasticity have been attributed to the NMDA receptor (*8-10*). Recently, one important study has added further insight into the functions of NR2 subunits *in vivo*. Mice expressing truncated NR2A, NR2B, and NR2C molecules, lacking their C-terminus intracellular motif, show similar phenotypes to those carrying total disruption of the corresponding genes (*11*). Although the truncated NR2 receptor subunits retain both ligand-binding and channel-forming domains, the results, unexpectedly,

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Abbreviations: Fas II, Fasciclin II; GuK, guanylate kinase; LTP, long-term potentiation; nNOS, neuronal nitric oxide synthase; NMDA, *N*-methyl-D-aspartate; PSD, postsynaptic density; PKC, protein kinase C; SH3, Src homology region 3; GAP, GTPase activating protein.

suggest that the subunits can hardly exert any function *in vivo* unless their C-terminal motif is maintained. These results imply that the C-terminal motif of the NMDA receptor subunits is essential for their function *in vivo*. The C-termini of these subunits are known to interact with PDZ domains (*12-14*). Therefore, it seems reasonable to speculate that PDZ proteins that associate with the C-termini of NR2 subunits are crucial for functional synaptic signaling *in vivo*.

Among various PDZ proteins, PSD-95, also called SAP90, was first reported to associate with the C-terminal motif of NR2 subunits of the NMDA receptor (*12, 14*). PSD-95/SAP90 was also reported to interact with some of the mammalian potassium channels (*15-17*). PSD-95/SAP90 is enriched in the postsynaptic density (PSD), after which it is named, and shows a structure related to the *Drosophila* tumor suppressor protein, DlgA (*4*). Both contain three PDZ domains (PDZ1-3) at the N-terminal side, a Src homology region 3 (SH3) domain in the middle, and a guanylate kinase-like (GuK) domain at the C-terminal end (Fig. 1). Several other synaptic proteins sharing structural similarity with PSD-95/SAP90 have since been identified. These include SAP102 (*18*) and PSD-93/Chapsyn-110 (*19, 20*) (Fig. 1). They are, all, referred to as Dlg-like PDZ proteins in this review.

PDZ domains of these Dlg-like PDZ proteins have been shown to recognize the common amino acid sequence at the partner's C-terminus; Serine/Threonine-X (any amino acid)-Valine (called tSXV motif). This C-terminal motif can be found in various membrane-associated molecules in the nervous system, as listed in Table I. Actually, yeast two-hybrid cloning and *in vitro* binding assays have revealed that a variety of molecules including the NMDA receptors and potassium channels, all of which carry the tSXV motif, can indeed interact with the Dlg-like PDZ proteins as well as with other PDZ proteins. Moreover, other glutamate receptors such as the metabotropic glutamate receptor 1/5 and AMPA-type glutamate receptors 2/3, whose C-termini are different from the tSXV motif, also interact with other PDZ proteins (*21, 22*). These suggest that PDZ proteins can interact with a large variety of synaptic proteins having or not having tSXV motif.

Our knowledge about functions of the PDZ proteins at the mammalian neuronal synapse is still limited. In the next chapter, functions of DlgA, a *Drosophila* PDZ protein at the neuromuscular synapse, will be reviewed with respect to development and organization of the synaptic junction.

Roles of DlgA in the *Drosophila* neuromuscular junction

The roles of DlgA, a *Drosophila* PDZ protein at the glutamatergic neuromuscular synapses, have been well characterized and have provided insight into the function of Dlg-like proteins at synapses of invertebrate and vertebrate brains. DlgA is encoded by the tumor suppressor gene discs-large (*dlg*) (*3*). It is expressed at specialized epithelial and neuromuscular junctions (*23*). At the neuromuscular junctions, the DlgA protein is localized at both pre- and postsynaptic sites (*23, 24*). Mutation in the *dlg* gene results in various abnormalities at neuromuscular synapses, such as poorly developed postsynaptic specialization, disrupted synaptic targeting of Shaker K^+ channel and enhanced synaptic transmission (*23-26*). This suggests significant roles for DlgA protein in the normal function and development of the neuromuscular synapse. Postsynaptic targeting or clustering of the Shaker K^+ channel appears to depend on PDZ domains of DlgA (*26*). The PDZ1 and PDZ2

TABLE I. **Cell surface molecules carrying a tSXV motif and their associated PDZ proteins in the nervous system.**

Protein	C-terminus	PDZ protein
K^+ channel (Kv1.4)	VSIETDV	PSD-95-related[a]
K^+ channel (Kv1.1)	SKLLTDV	
Ca^{2+} ATPase 4b	QSLETSV	PSD-95-related[a]
Na^+ channel (α subunit)	GVKESLV	Syntrophin
NMDAR2A	PSIESDV	PSD-95-related[a]
NMDAR2B	SSIESDV	PSD-95-related[a]
NMDAR1 variants	PSVSTVV	PSD-95-related[a]
Serotonin receptor 2A	NEKVSCV	
Serotonin receptor 2C	NEKVSCV	MUPP1
β1 adrenergic receptor	FSSESKV	
VIP receptor	QAEVSLV	
CRF receptor	IKQSTAV	
p75 NGF receptor	STATSPV	
V-CAM	EAQKSKV	
Protein kinase Cα	PILQSAV	PICK1
Neuroligin	SHSTTRV	PSD-95-related[a]

[a]Many molecules that bind to PSD-95/SAP90 can interact with other Dlg-like PDZ proteins including SAP97, SAP102, and PSD-93/Chapsyn-110. Several other molecules are reported to associate with PICK1 (*71*), MUPP1 (*72*), Syntrophin (*73*).

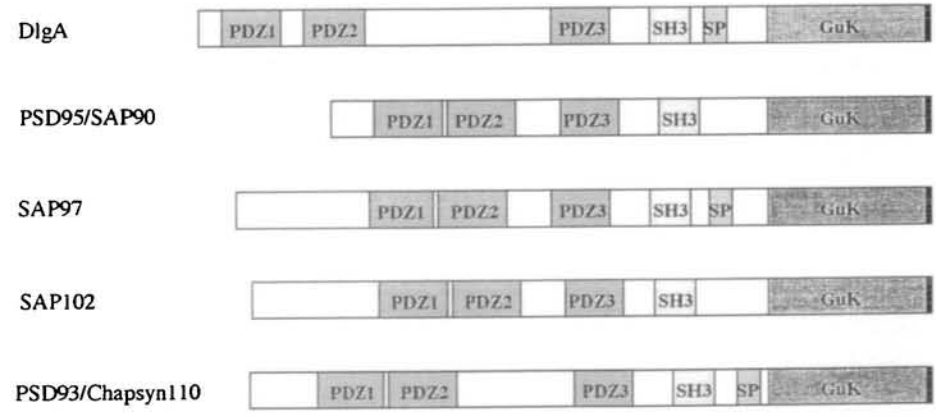

Fig. 1. **Structural similarity among Dlg-like PDZ proteins.** All the Dlg-like PDZ proteins contain three PDZ domains, one SH3 domain and one guanylate kinase (GuK) domain. A peptide sequence designated SP can be eliminated by alternative splicing. This figure is drawn with reference to the review on PDZ domains (*6*). Note: A novel protein, named S-SCAM (synaptic scaffolding molecule), has been isolated recently, which has an inverse structure of the Dlg-like PDZ proteins with a GuK-like domain at its N-terminal region and PDZ domains in its C-terminal portion. It binds SAPAP through the GuK-like domain and NMDA receptors and neuroligins through the PDZ domains (*74*).

domains in DlgA interact with the C-termini of Shaker K^+ channels, and these two PDZ domains are sufficient for clustering of the K^+ channel (*26*). The PDZ1 and PDZ2 cannot, however, localize the channel to the synapse. Neither are the SH3 nor the GuK domains in DlgA able to mediate such localization. Recently, a novel role of DlgA was elucidated. A cell-cell adhesion molecule, Fasciclin II (Fas II), also interacts with DlgA at the synapse (*27, 28*). Fas II is a cell surface molecule carrying the tSXV motif, expressed at both pre- and postsynaptic sites, and plays crucial roles in the structural stabilization of the neuromuscular synapse in *Drosophila* (*29*). A direct interaction between tSXV motif of Fas II and PDZ domains of DlgA is both necessary and sufficient for synaptic targeting of Fas II molecules (*27, 28*). Thus, during the development of *Drosophila* neuromuscular junction, the DlgA protein appears to play essential roles in stabilizing synapses structurally and in clustering and/or localizing Shaker K^+ channels to the postsynaptic sites by cross-linking various molecules in the synapse.

Multiple binding partners of Dlg-like PDZ proteins at the mammalian glutamatergic synapse

The PDZ domains recognize not only the core C-terminal peptide motif (tSXV) of partner molecules but also its flanking amino acid sequence. Thus, individual PDZ domains have different affinities to various C-terminal sequences (*7, 30*). Therefore, the binding specificity of individual PDZ domains in a Dlg-like PDZ protein may vary among various PDZ sequences. Interestingly, one PDZ domain in DlgA has higher homology to the corresponding PDZ domain in other Dlg-like PDZ proteins than with the other two PDZ domains in DlgA. In some cases, one Dlg-like PDZ protein can even substitute for another: Both mammalian SAP97 and SAP102 transgenes restore wild-type morphology to neuromuscular synapses in *Drosophila dlg* mutants (*31*).

In addition to binding to the C-terminal peptide motif, PDZ domains are known to interact with each other. Neuronal nitric oxide synthase (nNOS) contains one PDZ domain, and this domain interacts with the PDZ2 domain (but not PDZ1 nor PDZ3 domains) of PSD-95/SAP90 (*32*). In fact, nNOS and PSD-95/SAP90 are co-immunoprecipitated from membrane preparations (*32*). More recently, many novel molecules have been added to the list of proteins that can bind to PSD-95/SAP90 and/or other members of the Dlg family. These include the neuroligins (*33*), CRIPT (cysteine-rich interactor of PDZ3) (*34*), Ca^{2+}-ATPase 4b (*35*) and SynGAP (Synaptic GTPase activating protein) (*36*) (Fig. 2). Neuroligin was first identified as a molecule that binds to β-neurexin (a putative α-latrotoxin receptor at the presynaptic membrane). It also binds to the PDZ3 domain of PSD-95/SAP90 (*33*). Therefore, the trans-synaptic interaction of neuroligin and neurexin is proposed as a mechanism for recruiting the ion channels to the synaptic sites, or alternatively, might be involved in trans-synaptic signaling. The novel molecule, CRIPT, interacts with the same PDZ3 domain and with β-tubulin. This suggests a potential role in regulating cytoskeletal interactions with the postsynaptic membrane: CRIPT causes redistribution of PSD-95/SAP90 along microtubules in COS7 cells (*34*). In addition, the binding partners of the GuK-like domain in this Dlg-like PDZ protein have been identified recently. These are called SAPAPs (SAP90/PSD-95-associated proteins) or GKAP (guanylate kinase-associated protein), and shown to be co-immunoprecipitated with K^+ channel (*37, 38*). Altogether, these observations indicate the complex nature of the molecular interactions between Dlg-like PDZ proteins and many other signaling molecules (Fig. 2).

Synaptic targeting and clustering of NMDA receptors

Because of the highly compacted postsynaptic structures, results from immunohistochemical experiments regarding co-localization of synaptic proteins, including NMDA receptors, must be interpreted cautiously (*39*). PSD-95/SAP90 is mainly presynaptic at inhibitory γ-aminobutyric acid (GABA-ergic) synapses in the cerebellum (*40*). At forebrain synapses, however, PSD-95/SAP90 is associated with the postsynaptic, and not with the presynaptic, membrane (*41*). PSD-93/chapsyn-110 and SAP102 are also localized at the postsynaptic membrane in hippocampal excitatory synapses (*18-20*). In contrast, SAP97 is presynaptic at forebrain excitatory synapses (*42*). Since NMDA receptors are found at both pre- and postsynaptic sites (*43*), PSD-95/SAP90, PSD-93/chapsyn-110, SAP97, and SAP102 are all candidates for interaction with the NMDA receptor subunits *in vivo*. PSD-95/SAP90 and PSD-93/chapsyn-110 behave similarly with respect to the clustering of K^+ channels at synapses (*15, 20*). Thus, it remains unclear whether K^+ channels and NMDA receptors in the brain are authentic partner molecules to one or both of these PDZ proteins.

In the development of neuromuscular synapse, receptor

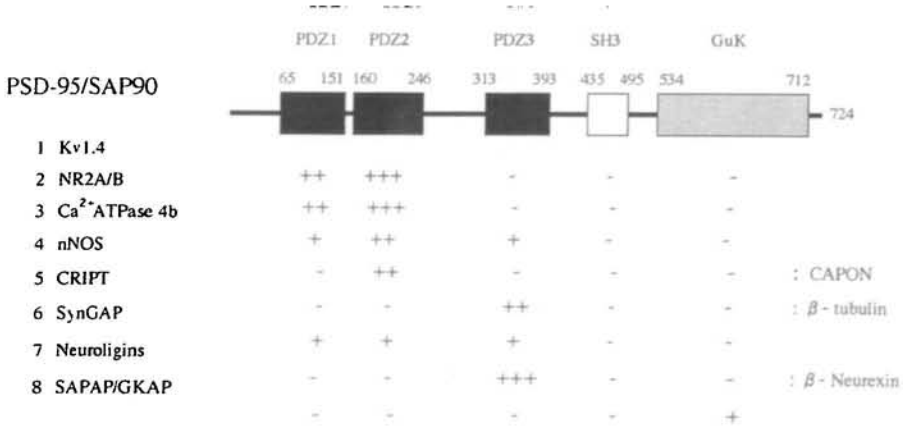

Fig. 2. **Binding partners to PSD-95/SAP-90.** Various molecules are shown to associate with the individual domains of PSD-95/SAP90 with different affinities. These molecules can also interact with other proteins as listed on the right side.

clustering is thought to be a molecular process distinct from receptor targeting (*1*). For example, an extracellular molecule, agrin, enhances the association among nicotinic acetylcholine receptor complexes and induces the formation of receptor aggregates that appear as a patch structure widely distributed on cell surfaces. Hsueh *et al.* (*44*) found that the clustering of K^+ channels only requires the N-terminal PDZ domains and/or the N-terminus of PSD-95/SAP90. The results proposed that channel clustering may depend on aggregation of PDZ domains which is achieved by disulfide-linked multimerization of PSD-95/SAP90 through the two cysteines at its N-terminus. This hypothesis is controversial, however, as the cysteine residues are now suggested to be palmitoylated in PSD-95/SAP90 (see below). Alternatively, these Dlg-like PDZ proteins can be multimerized by intermolecular concatenation of the PDZ domains. No partner for the SH3 domain of the Dlg-like PDZ proteins has yet been identified, however. The exact nature of their multimerization, if any, leading to the receptor clustering, remains to be elucidated.

A variety of PDZ proteins have been shown to interact with cytoskeletal structures (*45-48*) and this interaction is likely to be important for synaptic targeting and/or anchoring of receptors. The targeting of NR2 subunits appears not to require their tSXV motif: C-terminally truncated NR2 subunits can form glutamate-gated channels that are activated by synaptic inputs, just as are the wild-type subunits (*11*). Nevertheless, the tSXV motif of some NR1 splice variants (*49*) might contribute to targeting/anchoring the NMDA receptor complex to the synapse. The fact that the NMDA receptor is capable of being clustered in the absence of PSD-95/SAP90 and PSD-93/chapsyn-110 in cultured hippocampal cells (*50*), however, appears to negate this possibility. What, then, controls clustering and/or targeting of the NMDA receptor complex before it is anchored at the synapse with signal transducing molecule(s)? Some cytoskeleton-associated proteins, such as α-actinin-2 (*51*) and yotiao (*52*), which can directly interact with NMDA receptor channels but not through their C-termini, may provide an alternative targeting mechanism. α-Actinin-2, a protein known to cross-link actin filaments, can also be co-immunoprecipitated from brain tissue with NR1, NR2B, and PSD-95/SAP90 (*51*) and is colocalized with the NMDA receptor at synaptic sites in cultured hippocampal neurons (*50*). This suggests that α-actinin-2 may be responsible for anchoring NMDA receptor to synapses. In contrast, yotiao, also binds with NR1 through the region called the C1 cassette, which is subjected to alternative splicing and contains a site of phosphorylation by protein kinase C (PKC) (*49*). The C1 cassette also has high-affinity for calmodulin (*53, 54*). Interestingly, phosphorylation of the C1 cassette by PKC controls the subcellular targeting of NR1 subunits in heterologous cells (*55*). Since not all the NMDA receptor complexes, however, include the NR1 subunit containing the C1 cassette, the splicing pattern of this region in NR1 mRNA may influence subcellular localization of the NMDA receptor channels.

Assembly of signal transducing units with NMDA receptors

In mice carrying the C-terminally truncated NR2 subunits the NMDA synaptic current is normal. However, these truncated subunits fail to participate in some physiological events such as long-term potentiation (LTP) (*11*), suggesting ablated signal transduction relays. These results indicate that the Dlg-like PDZ protein(s) associated with C-termini of NR2 subunits may be responsible for assembling a signal transducing module in close vicinity to the receptor channel allowing rapid response following channel activation and cation influx. This assembly seems to be essential for NMDA receptor function because mice expressing C-terminally truncated NR2 subunits show a phenotype similar to those whose NR2 genes are fully disrupted (*11, 56-58*). What is, then, the signaling pathway downstream from the Dlg-like PDZ protein(s) that is perturbed in the mutant mice carrying the C-terminally truncated NR2 subunits? It is possible that the G-protein-coupled cascade and/or Ras-related signals comprise the downstream pathway from the synapse, as both have been suggested to interact with PDZ proteins (*36, 59*). SynGAP is a PDZ-interacting molecule that is highly homologous to RasGAP and, indeed, can activate Ras/GTPase (*36, 60*). In contrast to RasGAP, SynGAP is expressed only in the nervous system and is enriched at postsynaptic sites. These circumstantial pieces of evidence suggest that SynGAP might transduce signals from other PSD-95/SAP90-associated molecules, such as the NMDA-receptors and neuroligins, within the context of a PDZ domain-dependent signaling complex.

One of the other candidates for the downstream signaling is nNOS, which synthesizes nitric oxide (NO). nNOS is a calmodulin-regulated enzyme and NO formation is linked to NMDA receptor activity (*61*). nNOS contains a PDZ domain, through which it interacts with PSD-95/SAP90 and PSD-93/chapsyn-110 (*19, 32*). Moreover, the subcellular distribution of nNOS is altered if its PDZ domain is deleted (*32*). Thus, these PDZ proteins are likely to contribute to functional coupling between NMDA receptors and nNOS. It is not known, however, whether the PDZ domain of nNOS competes with NR2 for binding to the PDZ2 domain of PSD-95/SAP90. Mutant mice expressing C-terminally truncated NR2 subunits show more severe abnormalities than those carrying a disrupted nNOS gene (*62*). This observation supports the fact that the Dlg-like PDZ proteins attached to NMDA receptor channels must interact not only with nNOS but also with some other signal-transducing molecules. Recently, Jaffrey *et al.* (*63*) discovered a new molecule, CAPON (carboxyl terminal PDZ ligand of nNOS), by yeast two-hybrid screening. CAPON interacts with the sole PDZ domain of nNOS and can prevent PSD-95/SAP90 from binding to nNOS. It would be interesting to know whether the association of PSD-95/SAP90 or CAPON influences the activity of nNOS.

Palmitoylation of PDZ proteins

Palmitoylation refers to the post-translational covalent attachment of long-chain fatty acids, mostly palmitic acid, to the side chain of cysteine residues in proteins. It often involves the N-terminal cysteines, but internal cysteines can also be palmitoylated. It is unique among the lipid modifications of proteins (acylation), in that it is a reversible, dynamic and regulatable process (*64*). In recent years, many signal-transducing proteins such as G proteins and Src-like tyrosine kinases have been found to be palmi-

toylated and this has been shown to be essential for their association with the cell membrane in close proximity to receptors and ion channels (*65*). A recent report has indicated that PSD-95/SAP90 is a major palmitoylated protein at the postsynaptic membrane, and that the palmitoylated PSD-95/SAP90 is isolated from cell membrane fractions (*66*). Mutating the cysteines at position +3 and/or +5 of PSD-95/SAP90 inhibits its association with the cell membrane and results in a lack of interaction with K^+ channels (*66*). This work also demonstrated that the association of PSD-95/SAP90 with K^+ channels *in vivo* requires membrane targeting of PSD-95/SAP90 by palmitoylation. Palmitoylation thus seems to be responsible for increasing the local concentration of PSD-95/SAP90 at the postsynaptic membrane in the vicinity of ion channels and for modifying the accessibility of PSD-95/SAP90 to signaling molecules, ion channels or receptors. In fact, attaching a transmembrane domain to the N-terminal side of a mutated PSD-95/SAP90 (lacking two cysteine residues in its N-terminal region) can functionally substitute for palmitoylation and facilitate interaction with ion channels *in vivo* (*66*). Interestingly, SAP97 also associates with K^+ channels, even though SAP97 lacks N-terminal cysteines (*67*). However, their complexes are located in different subcellular region from those of PSD-95/SAP90: The K^+ channels bound to SAP97 are intracellular, while those associated with PSD-95/SAP90 are close to the cell membrane (*67*). From these results, it seems plausible that palmitoylation of PSD-95/SAP90 might be responsible not only for PSD-95's own targeting to specific subdomains in the cell membrane but also for the targeting of molecules associated with PSD-95/SAP90.

PSD-93/chapsyn-110 (*19, 20*), SAP102 (*18*), SAPAP1/GKAP, SAPAP2 and 3 (*37, 38*) as well as CRIPT (*34*), are among the PSD proteins having potential palmitoylation sites. PSD-93/chapsyn-110 has various isoforms that are produced by alternative splicing at its N-terminus (*19*). One of the isoforms has cysteines at positions 3 and 5 while the other's cysteines are at positions 5 and 7. SAPAP1/GKAP also exhibits such splicing variations at its N-terminus, and their pattern of alternative splicing is regulated during the development of the brain (*38*). Interestingly, the shorter variants lack potential palmitoylation sites, and the expression of their mRNAs increases with brain development in contrast to that of the longer variant, which decreases (*68*). It would be interesting, therefore, to clarify whether the above-mentioned proteins are subject to palmitoylation, whether palmitoylation is a regulatory step for their association with the synaptic membrane, and if this would affect the functional status of the synapse through differential targeting of various ion channel and receptor subunits to the synapse.

The reaction of palmitoylation is bi-directionally regulated by various agents and enzymes. In the case of heterotrimeric G-proteins, G-protein-coupled receptor activation with an agonist increases palmitate turnover, leading to an increase in the translocation of the Gα subunit from the cell membrane to the cytoplasm (*69*). NO is known to inhibit palmitoylation of G-proteins and GAP-43 in neurons (*70*). Thus, the complex of PSD-95-nNOS-NMDA receptor might couple calcium ion influx to NO production so to regulate the palmitoylation state of PSD-95/SAP90: PSD-95/SAP90 and/or other similarly palmitoylated proteins of the postsynaptic membrane is exposed to high levels of NO following activation of nNOS that is caused by an increased cation influx through the NMDA receptor. Therefore, depalmitoylation and/or inhibition of palmitoylation might help dissociate the protein in question from the membrane and modify its interaction with other partner molecules at the PSD.

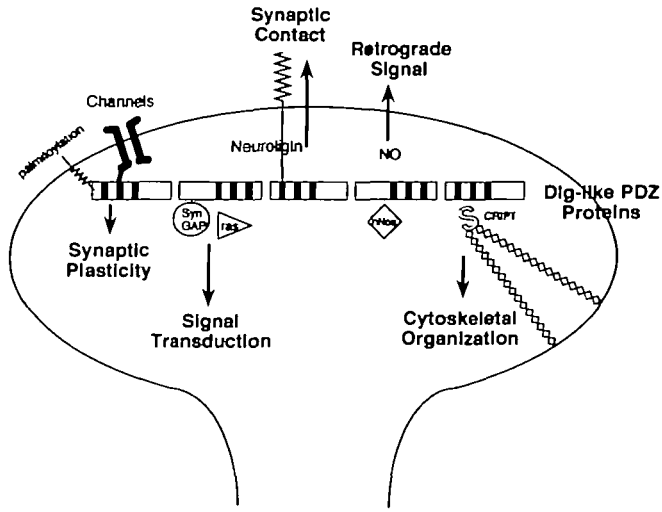

Fig. 3. **Putative functions of Dlg-like PDZ proteins: multiple interactions and their significance.**

Future directions

As mentioned above, it is surprising that a single PDZ protein can bind to many synaptic partner molecules and, conversely, that a single partner might interact with multiple PDZ proteins. How can we explain the redundancy of interactions of the Dlg-like PDZ proteins with their partner molecules? Given the variety of partner molecules and their various functions, these PSD proteins may form the basis for a variety of synaptic functions (Fig. 3). PDZ proteins might simply provide a docking platform for the synaptic machinery and facilitate their mutual interactions between signaling molecules at the synapse. Even if this is the case, individual synapses of single neurons can be functionally distinguished by having different PDZ proteins that carry a specific set of channels, receptors and adhesion molecules. The synaptic specificity marked with distinct PDZ proteins may contribute to the formation of Hebbian-type synapses that are activated selectively by different types of neuronal activities. Future studies promise to provide insight into how PDZ proteins are involved in synaptic development and synaptic plasticity, such as LTP.

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