

MINIREVIEW

# PDZ Protein Regulation of G Protein–Coupled Receptor Trafficking and Signaling Pathways

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## ABSTRACT

G protein–coupled receptors (GPCRs) contribute to the regulation of every aspect of human physiology and are therapeutic targets for the treatment of numerous diseases. As a consequence, understanding the myriad of mechanisms controlling GPCR signaling and trafficking is essential for the development of new pharmacological strategies for the treatment of human pathologies. Of the many GPCR-interacting proteins, postsynaptic density protein of 95 kilodaltons, disc large, zona occludens-1 (PDZ) domain–containing proteins appear most abundant and have similarly been implicated in disease mechanisms. PDZ proteins play an important role in regulating receptor and channel protein localization within synapses and tight junctions and function to scaffold intracellular signaling protein complexes. In the current study, we review the known functional interactions between PDZ domain–containing proteins and GPCRs and provide insight into the potential mechanisms of action. These PDZ domain–containing proteins include the membrane-associated guanylate-like kinases [postsynaptic density protein of 95 kilodaltons; synapse-associated protein of 97 kilodaltons; postsynaptic density protein of 93 kilodaltons; synapse-associated

protein of 102 kilodaltons; discs, large homolog 5; caspase activation and recruitment domain and membrane-associated guanylate-like kinase domain-containing protein 3; membrane protein, palmitoylated 3; calcium/calmodulin-dependent serine protein kinase; membrane-associated guanylate kinase protein (MAGI)-1, MAGI-2, and MAGI-3], Na<sup>+</sup>/H<sup>+</sup> exchanger regulatory factor proteins (NHERFs) (NHERF1, NHERF2, PDZ domain–containing kidney protein 1, and PDZ domain–containing kidney protein 2), Golgi-associated PDZ proteins (Gα-binding protein interacting protein, C-terminus and CFTR-associated ligand), PDZ domain–containing guanine nucleotide exchange factors (GEFs) 1 and 2, regulator of G protein signaling (RGS)–homology-RhoGEFs (PDZ domain–containing RhoGEF and leukemia-associated RhoGEF), RGS3 and RGS12, spinophilin and neurabin-1, SRC homology 3 domain and multiple ankyrin repeat domain (Shank) proteins (Shank1, Shank2, and Shank3), partitioning defective proteins 3 and 6, multiple PDZ protein 1, Tamalin, neuronal nitric oxide synthase, syntrophins, protein interacting with protein kinase C α 1, syntenin-1, and sorting nexin 27.

## Introduction

In the central nervous system, G protein–coupled receptors (GPCRs) and ion channels are targeted to the membrane of dendritic postsynaptic terminals in and around a region termed

the postsynaptic density (PSD) (Neubig and Siderovski, 2002; Feng and Zhang, 2009; Magalhaes et al., 2012). Each postsynaptic density is specifically organized, such that dozens to hundreds of receptors are targeted to this specialized membrane domain via the interaction of scaffolding proteins with the receptors. These scaffolding proteins contain multiple protein–protein interaction domains that allow them to interact with a multitude of structural and signaling proteins and hold them in close proximity with one another (Feng and Zhang, 2009). Of these scaffolding proteins, it is believed that postsynaptic

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**ABBREVIATIONS:** AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR, AMPA receptor; CAL, conductance regulator-associated ligand; CRF, corticotropin-releasing factor; ERK, extracellular signal-related kinase; GEF, guanine nucleotide exchange factor; GIPC, Gα-binding protein interacting protein carboxyl-terminus; GK, guanylate kinase-like domain; GPCR, G protein–coupled receptor; hIPR, human prostacyclin receptor; MAGI, membrane-associated guanylate kinase protein; MAGUK, membrane-associated guanylate kinase; mGluR, metabotropic glutamate receptor; MPP, membrane palmitoylated protein; NHERF, Na<sup>+</sup>/H<sup>+</sup> exchanger regulatory factor; NMDA, N-methyl-D-aspartate; NMDAR, NMDA receptor; nNOS, neuronal nitric oxide synthase; μOR, μ opioid receptor; Par, partitioning defective protein; PDZ, PSD-95, disc large, zona occludens-1; PH, pleckstrin-homology; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PSD, postsynaptic density; RGS, regulator of G protein signaling; SH3, SRC homology 3; Shank, SRC homology 3 domain and multiple ankyrin repeat domain; SSTR, somatostatin receptor.

density protein of 95 kilodaltons (PSD-95), disc large, zona occludens-1 (PDZ) domain-containing proteins are the most abundant and often provide direct contact with both GPCRs and ion channels at the postsynaptic density (Cheng et al., 2006; Feng and Zhang, 2009). PDZ proteins are not only important for targeting GPCRs to synapses, but they have an important role in regulating tight junctions and signaling protein complexes. In the current review, we will provide an overview of the growing understanding of the role of PDZ domain-containing proteins in the regulation of GPCR subcellular localization, endocytosis, trafficking, and signal transduction.

## PDZ Domains

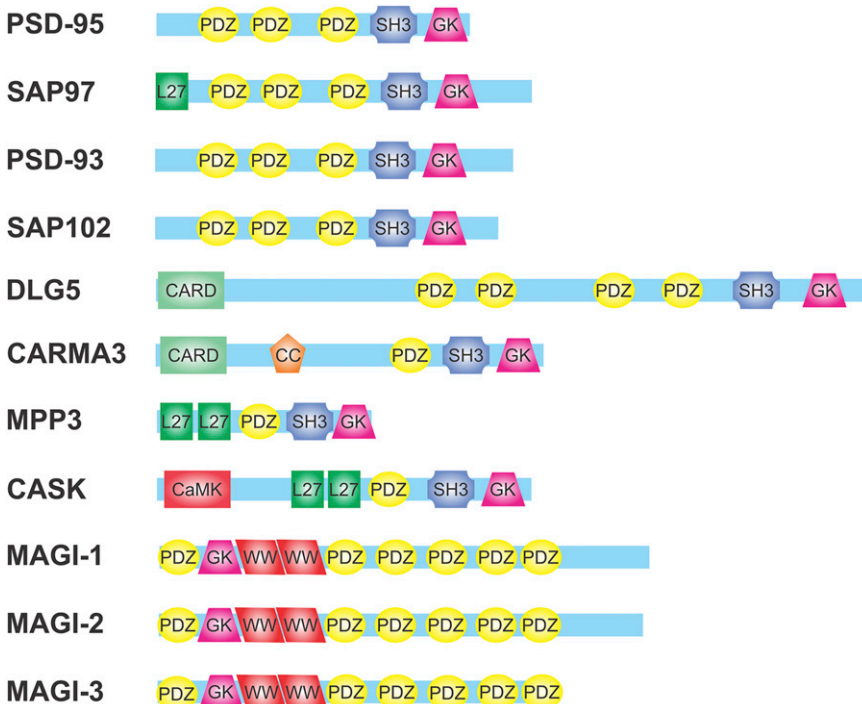
PDZ domains are approximately 80–90 amino acid residues in size and represent the most common protein-protein interaction domain (Doyle et al., 1996; Feng and Zhang, 2009; Magalhaes et al., 2012). Although there are hundreds of unique PDZ domain sequences, they all contain a conserved glycine-leucine-glycine-phenylalanine sequence that provides the domain's folded, globular, cup-like structure that is capable of recognizing short, finger-like peptides (Harris and Lim, 2001). Because of this structure, PDZ domains appear best suited for binding the distal regions of receptor carboxyl-terminal tails, which are labeled the PDZ-binding motif (Kornau et al., 1995; Niethammer et al., 1996; Harris and Lim, 2001; Magalhaes et al., 2012). Interestingly, additional studies have identified internal PDZ ligands that, like a carboxyl-terminal tail, project outwardly from the protein (Xu et al., 1998; Christopherson et al., 1999; Hillier et al., 1999; Fouassier et al., 2000; Harris and Lim, 2001; Paasche et al., 2005; Trejo, 2005). In this case, the internal PDZ-binding motif manifests as a sharply folded, finger-like projection.

## PDZ-Binding Motifs

Although seemingly imperfect and likely biased against internal PDZ ligands (reviewed by Trejo, 2005), a simple classification system has evolved to identify potential PDZ-binding motifs and helps to predict potential PDZ domain-containing protein interactions (Songyang et al., 1997; Bezprozvanny and Maximov, 2001; Sheng and Sala, 2001; Vaccaro and Dente, 2002). Although there is some deliberation over how many classes of PDZ-binding motifs there are, it is most commonly limited to three classes (Sheng and Sala, 2001; Tonikian et al., 2008; Magalhaes et al., 2012). Class I PDZ-binding motifs are the most described class within the literature and are classified by their final three-amino acid sequence of  $S/T-x-\varphi$ , where  $x$  indicates any amino acid and  $\varphi$  indicates any hydrophobic amino acid (Songyang et al., 1997; Bezprozvanny and Maximov, 2001; Sheng and Sala, 2001; Vaccaro and Dente, 2002). However, valine, isoleucine, or leucine appear to be the most common of the hydrophobic amino acids that contribute to the formation of a class I PDZ-binding motif (Songyang et al., 1997; Bezprozvanny and Maximov, 2001; Sheng and Sala, 2001; Vaccaro and Dente, 2002). Class II and III PDZ-binding motifs are not as well characterized and show slightly more ambiguous sequences, with class II having its final three amino acids as  $\varphi-x-\varphi$ , and class III having  $\Psi-x-\Psi$ , where  $\Psi$  represents any acidic amino acid residue (Sheng and Sala, 2001).

## GPCR-Interacting PSD-95 Family PDZ Domain-Containing Membrane-Associated Guanylate Kinase Proteins

**PSD-95 (DLG4).** PSD-95 contains three PDZ domains, an SRC homology 3 (SH3) domain, and a guanylate kinase-like (GK) domain (Fig. 1), and is prototypically localized within the



**Fig. 1.** Molecular topology of protein-protein interaction domains found in MAGUK family PDZ proteins. CaMKII,  $\text{Ca}^{2+}$ /calmodulin-dependent kinase domain; CARD, caspase activation and recruitment domain; CC, coiled-coiled domain; L27, L27 domain.

postsynaptic density (Sampedro et al., 1981; Cho et al., 1992). PSD-95 has been demonstrated to modulate both  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptor function as well as a number of GPCRs. With regards to AMPA and NMDA receptors, it appears that PSD-95 is important for enhancing and/or maintaining these receptors at the synaptic membrane, thereby potentiating receptor activation, channel opening, receptor-mediated currents, and receptor trafficking (Elias et al., 2006; Elias and Nicoll, 2007). PSD-95 is able to indirectly bind and regulate AMPA receptors via a shared association with transmembrane AMPA receptor-regulating proteins, such as stargazin (Chen et al., 2000). The  $\beta_1$ -adrenergic receptor ( $\beta_1$ AR) is the first GPCR to be reported as a PSD-95-interacting GPCR, and PSD-95 is responsible for antagonizing  $\beta_1$ AR endocytosis in response to agonist activation, thereby stabilizing the receptor at the cell surface (Hu et al., 2000) (Table 1). Despite the potentiation of  $\beta_1$ AR membrane expression, this interaction appears to have no functional consequence on  $G\alpha_s$ -coupled signaling, as measured by cAMP accumulation (Hu et al., 2000). In contrast, PSD-95 interactions with the serotonin 2A receptor (5-HT<sub>2A</sub>R)

facilitate  $G\alpha_q$ -coupled signaling by the receptor (Xia et al., 2003) (Table 2). PSD-95 has similarly been shown to antagonize the agonist-induced endocytosis of 5-HT<sub>2A</sub>R (Xia et al., 2003). G protein-coupled receptor kinase 5 phosphorylation also disrupts PSD-95 interactions with  $\beta_1$ AR, which is consistent with a PSD-95/ $\beta$ -arrestin competition model (Hu et al., 2002). Moreover, the recruitment of  $\beta$ -arrestin2 to 5-HT<sub>2A</sub>R corresponds with the dissociation of PSD-95, suggesting competitive binding for 5-HT<sub>2A</sub>R, with mechanistic implications for the regulation of endocytosis of PSD-95-associated GPCRs (Schmid and Bohn, 2010). Notably, PSD-95 is documented to have an opposing role in 5-HT<sub>2C</sub>R trafficking, where PSD-95 overexpression is suggested to suppress cell surface receptor expression and promote receptor endocytosis (Gavarini et al., 2006). This decrease in receptor expression at the cell surface is correlated with enhanced desensitization of 5-HT<sub>2C</sub>R-mediated Ca<sup>2+</sup> accumulation (Gavarini et al., 2006). In PSD-95 null mice, serotonin 2C receptor (5-HT<sub>2C</sub>R)-mediated *cfos* induction is impaired (Abbas et al., 2009). Despite significant sequence homology, PSD-95 appears to have opposing roles in regulating its trafficking and signaling pathways of 5-HT<sub>2A</sub>R and

TABLE 1  
Effect of PDZ proteins on GPCR trafficking

PDZ Protein	Trafficking Function	GPCR	Reference
PSD-95	↓ Endocytosis	$\beta_1$ AR, 5-HT <sub>2A</sub> R	Hu et al., 2000; Xia et al., 2003
	↑ Recycling	D <sub>1</sub> R	Sun et al., 2009
	↑ Membrane localization	GPR30	Akama et al., 2013; Broselid et al., 2014
SAP97	↑ Endocytosis	5-HT <sub>2C</sub> R, D <sub>1</sub> R	Gavarini et al., 2006; Zhang et al., 2007b
	↓ Endocytosis	CRFR1, 5-HT <sub>2A</sub> R	Dunn et al., 2013, 2014
	↑ Recycling	$\beta_1$ AR	Gardner et al., 2007
SAP102	↓ Mobility	A <sub>2A</sub> receptor	Thurner et al., 2014
MPP3	↑ Membrane localization	5-HT <sub>2C</sub> R	Gavarini et al., 2006
MAGI-2	↓ Endocytosis	VPAC1	Gee et al., 2009
	↑ Endocytosis	$\beta_1$ AR	Xu et al., 2001
NHERF1	↑ Membrane localization	mGluR1a	Sugi et al., 2007
	↓ Endocytosis	$\beta_2$ AR, TP $\beta$	Rochdi and Parent, 2003; Wang et al., 2007
	↑ Recycling	$\beta_2$ AR, human $\kappa$ opioid receptor	Cao et al., 1999; Li et al., 2002
	↑ Membrane localization	SSTR5, PTH1R	Wheeler et al., 2008; Bauch et al., 2014
	↑ Microvilli localization	Serotonin 4A receptor	Joubert et al., 2004
	↑ Cytoskeletal localization	Frizzled 4	Wheeler et al., 2011
	↑ Endocytosis	CCR5, platelet-activating factor receptor, P2Y <sub>12</sub> R	Hammad et al., 2010; Dupré et al., 2012; Nisar et al., 2012
PDZK1	↓ Endocytosis	5-HT <sub>2A</sub> R	Walther et al., 2015
	↑ Membrane localization	hIPR	Turner et al., 2011
PDZK2	↑ Membrane localization	hIPR	Reid et al., 2012
Shank1	↑ Clustering	mGluR5, CL1	Tu et al., 1999; Tobaben et al., 2000
Spinophilin	↓ Endocytosis	$\alpha_2$ AR	Brady et al., 2003
	↑ Endocytosis	$\mu$ OR	Charlton et al., 2008
MUPP1	↑ Membrane localization	5-HT <sub>2A</sub> R	Jones et al., 2009
	↑ Tight junction localization	SSTR3	Liew et al., 2009
Tamalin	↑ Membrane localization	mGluR1	Kitano et al., 2002; Sugi et al., 2007
	↑ Neurite localization	mGluR5	Kitano et al., 2002
Syntrophins	↑ Membrane localization	$\alpha_{1D}$ AR	Chen et al., 2006; Lyssand et al., 2008, 2011
	↑ Intracellular clustering	Prolactin-releasing peptide receptor	Lin et al., 2001; Madsen et al., 2012
	↓ Recycling	Growth hormone-releasing hormone receptor	Katsushima et al., 2013
Syntenin-1	↑ Membrane localization	G protein-coupled receptor 37 (endothelin receptor type B-like)	Dunham et al., 2009
SNX27	↑ Recycling	$\beta_2$ AR, $\beta_1$ AR, SSTR5	Lauffer et al., 2010; Temkin et al., 2011; Nakagawa and Asahi, 2013; Bauch et al., 2014
GIPC	↑ Endosome/Golgi localization	D <sub>2</sub> R, dopamine 3 receptor	Jeanneteau et al., 2004
	↑ Trafficking to early endosome	LPA <sub>1</sub> R	Varsano et al., 2012
	↑ Membrane stability	Human luteinizing hormone receptor	Hirakawa et al., 2003
CAL	↓ Membrane localization	$\beta_1$ AR, SSTR5	He et al., 2004; Bauch et al., 2014; Koliwer et al., 2015
	↓ Recycling	$\beta_1$ AR	Koliwer et al., 2015
	↑ Golgi localization	SSTR5	Wente et al., 2005; Bauch et al., 2014

TABLE 2  
Effect of PDZ proteins on GPCR signaling

PDZ Protein	Signaling Function	GPCR	Reference
PSD-95	↑ Inositol 1,4,5-trisphosphate ↑ cfos ↑ Desensitization of Ca <sup>2+</sup> ↓ or = cAMP	5-HT <sub>2A</sub> R 5-HT <sub>2C</sub> R 5-HT <sub>2C</sub> R D1R	Xia et al., 2003 Abbas et al., 2009 Gavarini et al., 2006 Zhang et al., 2007b; Sun et al., 2009
SAP97	↑ Inositol 1,4,5-trisphosphate ↑ ERK	5-HT <sub>2A</sub> R CRFR1, corticotropin-releasing factor receptor 2, 5-HT <sub>2A</sub> R	Dunn et al., 2014 Dunn et al., 2013, 2014
SAP102	↑ ERK	A <sub>A2</sub> R	Thurner et al., 2014
MPP3	↓ Desensitization of Ca <sup>2+</sup>	5-HT <sub>2C</sub> R	Gavarini et al., 2006
MAGI-2	↓ cAMP	VPAC1	Gee et al., 2009
MAGI-3	↑ ERK	Brain, LPA <sub>2</sub> R	Zhang et al., 2007a; Stephenson et al., 2013
NHERF1	↑ Rho	LPA <sub>2</sub> R	Zhang et al., 2007a
	↓ ERK	β <sub>1</sub> AR, β <sub>2</sub> AR	He et al., 2006; Yang et al., 2010
	↓ Desensitization of cAMP ↓ cAMP	PTH1R PTH1R	Wang et al., 2007 Wang et al., 2007; Wheeler et al., 2008
NHERF2	↑ Gα <sub>q</sub> coupling and activation ↑ ERK	PTH1R CCR5	Wang et al., 2010 Hammad et al., 2010; Kuang et al., 2012
	↑ Focal adhesion kinase, ↑ Rho ↓ β-catenin	CCR5 Fzd2/4	Kuang et al., 2012 Wheeler et al., 2011
	↑ Gα <sub>q</sub> coupling and PLC activation	PTH1R	Mahon et al., 2002; Wang et al., 2010
PDZK1	↑ Gα <sub>i</sub> coupling and ↓ AC activation	PTH1R	Mahon et al., 2002; Wang et al., 2010
	↑ PLC interaction ↑ Inositol 1,4,5-trisphosphate and ERK ↑ Ca <sup>2+</sup>	P2Y <sub>1</sub> , LPA <sub>2</sub> R LPA <sub>2</sub> R	Fam et al., 2005; Choi et al., 2010 Oh et al., 2004
	↑ PLC interaction and activation ↑ Inositol 1,4,5-trisphosphate	P2Y <sub>1</sub> , mGluR5	Fam et al., 2005; Paquet et al., 2006
	↑ Ca <sup>2+</sup> ↑ ERK	SSTR5 SSTR5, 5-HT <sub>2A</sub> R	Kim et al., 2012 Kim et al., 2012; Walther et al., 2015
PDZK2	↑ cAMP	hIPR	Turner et al., 2011
	↑ cAMP	hIPR	Reid et al., 2012
	↑ Ca <sup>2+</sup> and ERK	mGluR1/5	Sala et al., 2005
Shank1	↑ ERK and CREB phosphorylation	mGluR5	Verpelli et al., 2011
Shank3	↑ PLC interaction	Bradykinin 2 receptor	Choi et al., 2010
Par3	↓ Ca <sup>2+</sup>	α <sub>2</sub> AR, M <sub>1</sub> R, M <sub>3</sub> R	Wang et al., 2005; Fujii et al., 2008; Kurogi et al., 2009; Ruiz de Azua et al., 2012
Spinophilin	↓ Gα <sub>i</sub> coupling ↑ cAMP ↑ Gα <sub>i</sub> coupling	α <sub>2</sub> AR, A <sub>1</sub> R IPR μOR	Lu et al., 2010; Chen et al., 2012 Ma et al., 2012 Charlton et al., 2008; Fourla et al., 2012
MUPP1	↓ or ↑ ERK	μOR	Charlton et al., 2008; Fourla et al., 2012
	↑ Gα <sub>i</sub> coupling ↓ ERK	δ Opioid receptor δ Opioid receptor	Fourla et al., 2012 Fourla et al., 2012
	↓ Gα <sub>i</sub> coupling ↑ Ca <sup>2+</sup> ↑ Ca <sup>2+</sup> decay	Melatonin 1 receptor γ-Aminobutyric acid B receptor	Guillaume et al., 2008 Balasubramanian et al., 2007
nNOS	↑ Ca <sup>2+</sup> decay ↑ PKC interaction	Olfactory receptor 2AG1 μOR, serotonin 1A receptor, 5-HT <sub>2A</sub> R, D <sub>2</sub> R, M <sub>4</sub> R, cannabinoid receptor 1	Dooley et al., 2009 Sanchez-Blazquez et al., 2012
Syntrophins	↑ Inositol 1,4,5-trisphosphate, Ca <sup>2+</sup> and ERK	α <sub>1D</sub> AR	Lyssand et al., 2008, 2011
PICK1	↓ cAMP	Growth hormone-releasing hormone receptor	Katsushima et al., 2013
Syntenin-1	↑ c-Jun, CDC42, and PKCα	Frizzled-7	Luyten et al., 2008
GIPC	↓ Gα <sub>i</sub> coupling ↑ Protein kinase B	Dopamine 3 receptor LPA <sub>1</sub> R	Jeanneteau et al., 2004 Varsano et al., 2012
CAL	↓ ERK	β <sub>1</sub> AR	Hu et al., 2003
	↓ ERK	mGluR1, β <sub>1</sub> AR	Zhang et al., 2008b; Koliwer et al., 2015
PDZ-GEF1	↑ Ras ↑ ERK	β <sub>1</sub> AR Pituitary adenylate cyclase-activating polypeptide 1 receptor	Pak et al., 2002 Emery et al., 2013

(continued)

TABLE 2—Continued

PDZ Protein	Signaling Function	GPCR	Reference
LARG	↑ Rho	Angiotensin II receptor 1, sphingosine-1-phosphate receptor 2, endothelin 1 receptor, M <sub>1</sub> R, G2 accumulation protein/G protein-coupled receptor 132, histamine 1 receptor, thromboxane A2 receptor, proto-oncogene mas	Booden et al., 2002; Ying et al., 2006; Chiu et al., 2012; Medlin et al., 2010; Pfreimer et al., 2012; Artamonov et al., 2013; Del Galdo et al., 2013
PDZ-RhoGEF	↑ Rho	Gastrin-releasing peptide receptor	Patel et al., 2014
RGS3	↓ Gα <sub>q</sub> and Gα <sub>11</sub> activation ↓ Inositol 1,4,5-trisphosphate	Pheromone p-factor receptor M <sub>3</sub> R, gonadotropin-releasing hormone receptor, LHR, Follicle-stimulating hormone receptor, protease-activated receptor 1	Ladds et al., 2007 Neill et al., 1997, 2001; Castro-Fernandez and Conn, 2002; Castro-Fernandez et al., 2002, 2004; Anger et al., 2004; Tovey and Willars, 2004; Karakoula et al., 2008; Chen et al., 2014
	↓ Diacylglycerol	M <sub>3</sub> R, gonadotropin-releasing hormone receptor	Karakoula et al., 2008
	↓ Ca <sup>2+</sup>	M <sub>3</sub> R, endothelin 1 receptor	Dulin et al., 1999; Tovey and Willars, 2004
	↓ ERK	M <sub>2</sub> R, M <sub>3</sub> R, chemo-attractant C5a receptor, endothelin 1 receptor	Dulin et al., 1999; Wang et al., 2002; Anger et al., 2007; Nishiura et al., 2009
	↓ Protein kinase B ↓ cAMP	M <sub>2</sub> R, M <sub>3</sub> R LHR, follicle-stimulating hormone receptor	Anger et al., 2007 Castro-Fernandez et al., 2004
	↓ Gα <sub>i</sub> -mediated signaling	μOR, D <sub>2</sub> R, β <sub>2</sub> AR	Potenza et al., 1999; Chakir et al., 2011
	↑ Gα <sub>s</sub> -mediated signaling	β <sub>2</sub> AR	Chakir et al., 2011

5-HT<sub>2C</sub>R (Xia et al., 2003; Gavarini et al., 2006). PSD-95 was recently suggested to form a complex with G protein-coupled receptor 30, protein kinase A (PKA)-anchoring protein 5, and the PKA RIIβ regulatory subunit, thereby promoting G protein-coupled receptor 30 membrane localization and facilitating the constitutive inhibition of cAMP (Akama et al., 2013; Broselid et al., 2014). PSD-95 has also been reported to positively regulate dopamine 1 receptor (D<sub>1</sub>R) endocytosis and inhibit D<sub>1</sub>R-mediated cAMP formation (Zhang et al., 2007b). A more recent study suggests that PSD-95 contributes to D<sub>1</sub>R recycling and resensitization without influencing D<sub>1</sub>R-mediated Gα<sub>s</sub> activation (Sun et al., 2009). However, the methods and cellular contexts used to arrive at these conclusions in these various studies are not directly comparable. Nevertheless, this highlights the importance of considering the specific GPCR in question when determining the regulatory role of a PDZ domain-containing protein as well as the endogenous trafficking and signaling machineries available within each specific cellular context.

**Synapse-Associated Protein of 97 kDa (DLG1).** Although synapse-associated protein of 97 kDa (SAP97) shares ~60% sequence homology with PSD-95 (including three PDZ domains, an SH3 domain, a GK domain, and an additional L27 domain on the amino terminal), less is known about the role of SAP97 in regulating GPCR activity (Fig. 1). Nevertheless, SAP97 has been demonstrated to promote β<sub>1</sub>AR phosphorylation via cyclic AMP-dependent protein kinase (PKA), despite having no effect on β<sub>1</sub>AR-stimulated adenylyl cyclase activation and cAMP accumulation (Gardner et al., 2007). Additionally, SAP97 promotes recycling of β<sub>1</sub>AR by a mechanism that involves the formation of a complex among β<sub>1</sub>AR, PKA-anchoring protein 79, and PKA (Gardner et al., 2007; Nooh, et al., 2013, 2014). In contrast, SAP97 promotes membrane stabilization of the corticotropin-releasing factor

(CRF) receptor 1 by suppressing CRFR1 endocytosis (Dunn et al., 2013). Although SAP97 does not contribute to the regulation of CRFR1-mediated cAMP accumulation via Gα<sub>s</sub>, endogenous SAP97 is essential for CRF-mediated extracellular signal regulated kinase (ERK) 1/2 phosphorylation via the ERK1/2 signaling pathway (Dunn et al., 2013). In contrast, similar to what is observed for PSD-95-mediated enhancement of 5-HT<sub>2A</sub>R-stimulated inositol phosphate formation, the loss of endogenous SAP97 expression results in a reduction in 5-HT<sub>2A</sub>R-activated inositol accumulation via Gα<sub>q</sub> (Xia et al., 2003; Dunn et al., 2014). However, SAP97 also suppresses 5-HT<sub>2A</sub>R endocytosis and facilitates 5-HT-mediated ERK1/2 phosphorylation. The role of endogenous SAP97 in facilitating CRFR1- and 5-HT<sub>2A</sub>R-stimulated ERK1/2 phosphorylation does not require interactions with the PDZ-binding motifs of these receptors, and knockdown of endogenous SAP97 also reduces corticotropin-releasing factor receptor 2-mediated ERK1/2 phosphorylation (Dunn et al., 2013, 2014). Since corticotropin-releasing factor receptor 2 does not encode a class I PDZ-binding motif, it is possible that SAP97 may play a global role in regulating GPCR-mediated ERK1/2 activity that is independent of receptor interactions.

**PSD Protein of 93 kDa (DLG2) and SAP of 102 kDa (DLG3).** Postsynaptic density protein of 93 kDa (PSD-93) contains three PDZ domains, an SH3 domain, and a GK domain (Fig. 1). Not a great deal is known about the role of PSD-93 in regulating GPCRs, but PSD-95 and PSD-93 have been previously demonstrated to compensate for one another (Sun and Turrigiano, 2011). Therefore, it is likely that both PSD-93 and PSD-95 may play similar roles with respect to GPCR regulation. PSD-95 and PSD-93 have been identified to interact with the somatostatin receptor (SSTR) 1 and SSTR4 (Christenn et al., 2007), and both have been shown to inhibit NMDA receptor (NMDAR) endocytosis (Lavezzari et al., 2003).

Future studies are needed to examine the role of PSD-93 in the regulation of GPCR trafficking to determine whether its function overlaps with both PSD-95 and SAP97. Synapse-associated protein of 102 kDa (SAP102) contains three PDZ domains, an SH3 domain, and a GK domain (Fig. 1). SAP102 has been demonstrated to regulate adenosine A<sub>2A</sub> receptor mobility and promote A<sub>2A</sub> receptor-mediated ERK signaling (Thurner et al., 2014). SAP102 has additionally been identified to regulate the trafficking of AMPA and NMDA receptors. Thus, it is of interest in the future to determine whether SAP102 plays a role similar to that of other membrane-associated guanylate kinase (MAGUK) proteins in the regulation of GPCR activity.

**Discs, Large Homolog 5.** Discs, large homolog 5 (DLG5) differs from the common topology of the PSD-95 subfamily of MAGUKs, with the inclusion of an amino-terminal caspase activation and recruitment domain, which is similar to the caspase activation and recruitment domain and membrane-associated guanylate-like kinase domain-containing proteins, and a fourth PDZ domain (de Mendoza et al., 2010) (Fig. 1). CARMA3 has been implicated in facilitating GPCR-induced activation of NF $\kappa$ B via lysophosphatidic acid, endothelin-1, and angiotensin II (Scudiero et al., 2014). Although there does not appear to be any examples of DLG5 in the direct regulation of GPCRs, DLG5 has been implicated in regulating synaptogenesis by enhancing the membrane localization of the transmembrane protein N-cadherin (Wang et al., 2014). DLG5 has also been demonstrated to scaffold atypical protein kinase C (PKC) isoforms, and this provides a mechanism by which DLG5 contributes to the regulation of GPCR-mediated signaling (Nechiporuk et al., 2013).

### Other GPCR-Interacting PDZ Domain-Containing MAGUK Proteins

**Membrane Palmitoylated Proteins and Calmodulin-Activated Serine/Threonine Kinase (PALS3, LIN-2).** Membrane palmitoylated proteins (MPPs) (MPP1/p55, MPP2, MPP3, MPP4, MPP5/PALS1, MPP6/PALS2, and MPP7) are unified by the inclusion of a PDZ domain, an SH3 domain, and a GK domain (Fig. 1). Additionally, all but MPP1 have two amino-terminal L27 domains, with MPP5 also including an amino-terminal coiled-coil domain. MPP1 and MPP2 and MPP5–MPP7 also include a HOOK domain between their SH3 and GK domains. Although MPP proteins are a relatively abundant group of MAGUK proteins, very little is known about their regulation of GPCR function. MPP3 has been demonstrated to promote the membrane stability of 5-HT<sub>2C</sub>R and prevent receptor desensitization (Gavarini et al., 2006). MPP1 has additionally been implicated in membrane organization, raft formation, and receptor tyrosine kinase-mediated ERK signaling (Łach et al., 2012; Biernatowska et al., 2013). Thus, it is plausible that MPPs may generally promote the membrane organization of integral proteins, including GPCRs.

Ca<sup>2+</sup>/calcium/calmodulin-dependent serine protein kinase (CASK) is very similar in topology to the MPPs, with protein domains that include a catalytically active Ca<sup>2+</sup>/calmodulin-dependent kinase domain at the amino-terminus followed by two L27 domains, a PDZ domain, an SH3 domain, and a GK domain (te Velthuis et al., 2007; Mukherjee et al., 2008) (Fig. 1). CASK forms a tripartite complex with the PDZ domain

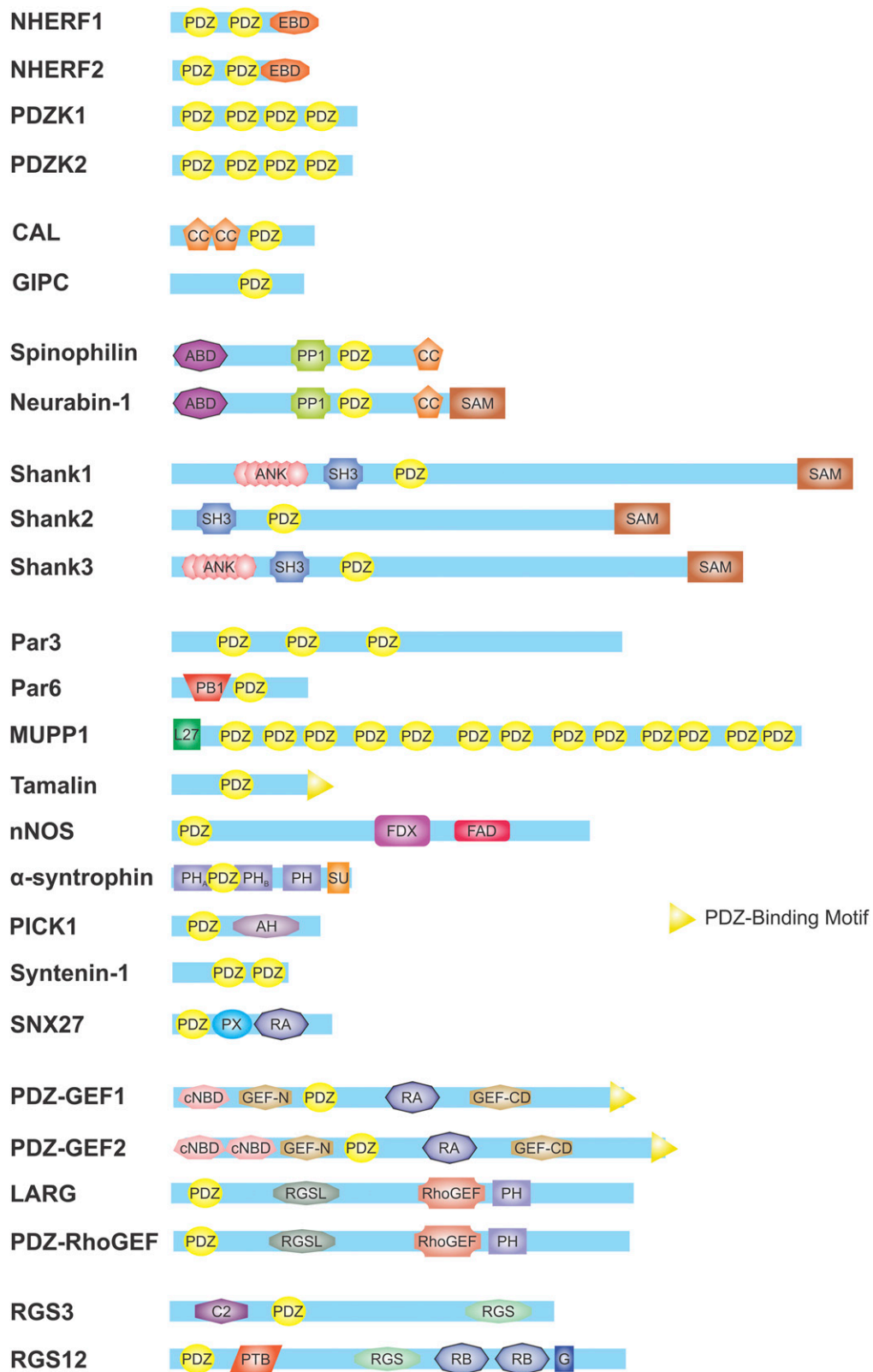
containing Mint1 and Veli proteins, but the role of Mint1 and Veli proteins in the regulation of GPCRs remains undetermined (Butz et al., 1998). Like MPP3, CASK has been shown to interact with 5-HT<sub>2C</sub>R (Bécamel et al., 2002, 2004; Gavarini et al., 2006). Although the functional consequence of this interaction on 5-HT<sub>2C</sub>R trafficking and signaling remains to be tested, CASK has been implicated in regulating the trafficking of NMDAR and AMPA receptor (AMPA), partly via its regulation of SAP97 conformation and receptor interactions (Jeyifous et al., 2009; Lin et al., 2013). Interestingly, CASK has been demonstrated to interact with PKA, PKC $\epsilon$ , and the regulator of G protein signaling (RGS) 4, which may suggest a role for CASK in regulating GPCR-mediated signaling (Hong and Hsueh, 2006).

### Membrane-Associated Guanylate Kinase with Inverted Orientation PDZ Protein Family

Membrane-associated guanylate kinase with inverted orientation proteins (MAGIs) include three proteins with an amino terminal PDZ domain followed by a GK domain, two tryptophan-tryptophan (WW) domains, and five more PDZ domains (Fig. 1). MAGI proteins differ from other MAGUK proteins in the exclusion of an SH3 domain (Dobrosotskaya et al., 1997). MAGI-1 colocalizes with the brain angiogenesis inhibitor 1 receptor (BAI-1R) at the cell membrane via an interaction with the receptor carboxyl-terminal tail, and MAGI-3 interacts with BAI-1R to promote ERK phosphorylation (Shiratsuchi et al., 1998; Stephenson et al., 2013). MAGI-3 promotes ERK and RhoA signaling, which is mediated by lysophosphatidic acid receptor 2 (LPA<sub>2</sub>R), but antagonizes ERK1/2 activation in response to the activation of either  $\beta_1$ AR or  $\beta_2$ AR (He et al., 2006; Zhang et al., 2007a; Yang et al., 2010). MAGI-2 interacts with  $\beta_1$ AR via its first PDZ domain and functions to promote  $\beta_1$ AR endocytosis without affecting  $\beta_1$ AR-mediated cAMP signaling (Xu et al., 2001). In contrast, MAGI-2 interacts with the vasoactive intestinal peptide receptor 1 (VPAC1) and functions to both inhibit VPAC1 endocytosis and suppress VPAC1-mediated cAMP signaling (Gee et al., 2009). MAGI-2 also promotes the cell surface expression of metabotropic glutamate receptor (mGluR) 1a via its association with the PDZ domain-containing protein tamalin (Sugi et al., 2007). Thus, similar to what has been reported for PSD-95 family PDZ proteins, the MAGI family of PDZ proteins contributes to the regulation of the endocytosis and cell signaling of a number of GPCRs, but the functional effects of these protein interactions have differential effects, depending on the GPCR studied.

### Na<sup>+</sup>/H<sup>+</sup> Exchanger Regulatory Factor Family of PDZ Proteins

**Na<sup>+</sup>/H<sup>+</sup> Exchanger Regulatory Factor 1.** Na<sup>+</sup>/H<sup>+</sup> exchanger regulatory factor (NHERF) 1 (ezrin/radixin/moesin-binding protein 50) is a relatively small PDZ domain-containing protein characterized by two PDZ domains and a carboxyl-terminal ezrin-binding domain (Fig. 2). NHERF1 represents one of the earliest PDZ proteins to be shown to interact with a GPCR (Hall et al., 1998). NHERF1 regulates Na<sup>+</sup>/H<sup>+</sup> exchange via its interaction with  $\beta_2$ AR without altering cAMP signaling, and has since been demonstrated to regulate a



**Fig. 2.** Molecular topology of other PDZ domain-containing proteins that interact with GPCRs. ABD, actin binding domain; AH, arfapatin homology domain; ANK, ankyrin repeat domain; C2, C2 domain; CC, coiled-coiled domain; cNBD, cyclic nucleotide binding domain; EBD, ezrin-binding domain; FAD, flavin adenine dinucleotide-binding domain; FDX, flavodoxin-like domain; G, Golocco motif; GEF-CD, Ras GEF catalytic domain; GEF-N, Ras-like GEF, N-terminal domain; L27, L27 domain; PB1, Phox/Bem1 domain; PH<sub>A/B</sub>, interrupted pleckstrin homology domain; PP1, protein phosphatase 1-binding domain; PTB, phosphotyrosine-binding domain; PX, Phox-homology domain; RA, Ras association domain; RGSL, RGS-like domain; RhoGEF, RhoGEF domain; SAM, sterile alpha motif; SU, syntrophin unique domain.

number of GPCRs. NHERF1 regulates the recycling of  $\beta_2$ AR, and its binding to the receptor is disrupted by G protein-coupled receptor kinase phosphorylation of  $\beta_2$ AR at serine residue 411 (Cao et al., 1999). However, NHERF1 is reported to inhibit recycling of the parathyroid 1 receptor (PTH1R) (Wang et al., 2007). NHERF1 also inhibits PTH1R desensitization and endocytosis, a function that appears to involve NHERF1-dependent inhibition of  $\beta$ -arrestin2 recruitment to PTH1R (Wang et al., 2007, 2009). NHERF1 expression also enhances PTH1R-mediated cAMP signaling and couples PTH1R to the activation of  $G\alpha_q$  (Wang et al., 2007, 2010; Wheeler et al., 2008). NHERF1 expression enhances cell surface expression of the  $\kappa$  opioid receptor, inhibiting downregulation and promoting receptor recycling (Li et al., 2002). In contrast, NHERF1 increases thromboxane receptor  $\beta$  cell surface expression by blocking the internalization of the receptor (Rochdi and Parent, 2003). An additional mechanism by which NHERF1 may increase GPCR membrane targeting is via its competition with the cystic fibrosis transmembrane conductance regulator-associated ligand (CAL) to antagonize CAL-mediated retention of GPCRs in the Golgi (Bauch et al., 2014).

In contrast to the role of NHERF1 in antagonizing the endocytosis of PTH1R and thromboxane receptor  $\beta$ , NHERF1 is reported to facilitate the endocytosis of a number of GPCRs. NHERF1 enhances chemokine (C-C motif) receptor 5 (CCR5) endocytosis and  $\beta$ -arrestin1 recruitment, thereby promoting the activation of ERK, Rho, and focal adhesion kinase signaling pathways, as well as potentially contributes to CCR5-mediated HIV-1 entry (Hammad et al., 2010; Kuang et al., 2012). NHERF1 overexpression also rescues the endocytosis of an internalization-defective platelet-activating factor receptor and antagonizes platelet-activating factor receptor-mediated inositol phosphate formation (Dupré et al., 2012). Agonist activation of the purinergic P2Y<sub>12</sub> receptor results in the  $\beta$ -arrestin-dependent recruitment of NHERF1 to the receptor and promotes the formation of a P2Y<sub>12</sub> receptor/NHERF1 complex that does not require PDZ-binding motif interactions (Nisar et al., 2012). NHERF1 also regulated frizzled family receptor activity (Wheeler et al., 2011). Thus, NHERF1 appears to play an integral, but complex, role in regulating the endocytosis and recycling of a variety of different GPCRs.

**Na<sup>+</sup>/H<sup>+</sup> Exchanger Regulatory Factor 2.** The topology of Na<sup>+</sup>/H<sup>+</sup> exchanger regulatory factor 2 (NHERF2) is quite similar to NHERF1 as it shares a 44% sequence homology with NHERF1 and contains two PDZ domains and a carboxyl-terminal ezrin-binding domain (Ardura and Friedman, 2011) (Fig. 2). Similar to NHERF1, NHERF2 contributes to the regulation of PTH1R (Mahon et al., 2002; Wang et al., 2010). NHERF2 functions to antagonize PTH1R coupling to  $G\alpha_s$ -coupling, while concomitantly promoting the coupling of PTH1R to both the activation of  $G\alpha_q$  and  $G\alpha_i$  (Mahon et al., 2002; Wang et al., 2010). NHERF2 also interacts directly with phospholipase C (PLC)  $\beta$  to enhance P2Y<sub>1</sub> receptor-mediated Ca<sup>2+</sup> signaling (Fam et al., 2005). Similarly, NHERF2 interacts with PLC $\beta$ 3 and the LPA<sub>2</sub>R, allowing for the formation of a protein complex that directly links the receptor to PLC $\beta$ 3-mediated inositol phosphate signaling (Oh et al., 2004; Choi et al., 2010). NHERF2 and mGluR5 show overlapping expression in a mouse brain at postsynaptic neuronal sites and astrocytic processes, and NHERF2 prolongs the mGluR5-mediated Ca<sup>2+</sup> response (Paquet et al., 2006).

**PDZ Domain-Containing Kidney Protein 1 (Na<sup>+</sup>/H<sup>+</sup> Exchanger Regulatory Factor 3) and 2 (Na<sup>+</sup>/H<sup>+</sup> Exchanger Regulatory Factor 4).** PDZ domain-containing kidney protein 1 (PDZK1), formerly known as Na<sup>+</sup>/H<sup>+</sup> exchanger regulatory factor 3, differs from NHERF1 and NHERF2 in structural topology by having four PDZ domains and no carboxyl-terminal ezrin-binding domain (Fig. 2). Nevertheless, PDZK1 has been implicated in regulating a subset of GPCRs. PDZK1 promotes the formation of a complex between SSTRs and PLC $\beta$ 3, similar to what is observed for LPA<sub>2</sub>R (Oh et al., 2004; Choi et al., 2010), thereby facilitating somatostatin-stimulated PLC activation, Ca<sup>2+</sup> mobilization, and ERK1/2 phosphorylation (Kim et al., 2012). PDZK1 also functions to enhance human prostacyclin receptor (hIPR) cell surface localization and cAMP signaling and contributes to endothelial cell migration and angiogenesis (Turner et al., 2011). PDZK1 inhibits 5-HT<sub>2A</sub>R endocytosis, and siRNA knockdown of PDZK1 results in reduced 5-HT<sub>2A</sub>R-mediated inositol phosphate accumulation, but is not involved in 5-HT<sub>2A</sub>R-stimulated ERK1/2 phosphorylation (Walther et al., 2015). However, PDZK1 interactions with 5-HT<sub>2A</sub>R do not appear to be required for its regulation of 5-HT<sub>2A</sub>R activity. In contrast, although PDZK1 does not regulate CRFR1-mediated cAMP accumulation, unlike what is observed for 5-HT<sub>2A</sub>R, PDZK1 facilitates CRFR1-mediated ERK1/2 phosphorylation. Similar to PDZK1, PDZ domain-containing kidney protein 2 (PDZK2) also has four PDZ domains and has been shown to regulate hIPR (Reid et al., 2012). Agonist activation of hIPR increases PDZK2 association and results in PKA- and PKC-mediated phosphorylation of PDZK2 (Reid et al., 2012). Like PDZK1, PDZK2 also enhances hIPR cell surface expression and cAMP accumulation (Reid et al., 2012). Taken together, PDZK1 and PDZK2 appear to be important for regulating the trafficking of an increasing subset of GPCRs and may be biased toward increased  $G\alpha_q$  signaling, similar to what is observed for both NHERF1 and NHERF2.

## PDZ Proteins that Regulate Golgi Trafficking

**G $\alpha$ -Binding Protein Interacting Protein Carboxyl-Terminus (TIP-2, Synectin).** RGS  $G\alpha$ -binding protein-interacting protein carboxyl-terminus (GIPC) is a PDZ domain-containing protein, with one PDZ domain that is implicated in the sorting of nascent proteins from the Golgi network (Liu et al., 2001) (Fig. 2). With regards to GPCRs, GIPC has been shown to target D<sub>2</sub>R to endosomes and the Golgi apparatus (Jeanneteau et al., 2004). Furthermore, GIPC expression suppresses dopamine 3 receptor  $G\alpha_i$ -coupling and prevents dopamine 3 receptor degradation (Jeanneteau et al., 2004). GIPC also plays a role in regulating both the human luteinizing hormone receptor and LPA<sub>1</sub>R trafficking (Hirakawa et al., 2003; Varsano et al., 2012). The interaction of GIPC with LPA<sub>1</sub>R is essential for LPA<sub>1</sub>R trafficking from APPL-positive signaling endosomes to early endosome antigen 1-positive early endosomes (Varsano et al., 2012). Additionally, GIPC links LPA<sub>1</sub>R to the protein kinase B signaling pathway, cell proliferation, and cell motility (Varsano et al., 2012). GIPC also contributes to the suppression of  $\beta_1$ AR-mediated ERK activation, but does affect  $\beta_1$ AR-stimulated cAMP accumulation (Hu et al., 2003).

**CAL (Golgi-Associated Coiled-Coil and PDZ Domain-Containing Protein, PIST).** CAL is also named Golgi-associated coiled-coil and PDZ domain-containing protein due to its common subcellular localization within the trans-Golgi



network and a structural topology consisting of two coiled-coil domains and one PDZ domain (Fig. 2). CAL is selectively localized to the trans-Golgi network in neurons as well as other cell types and interacts with Rab6a, a small GTPase implicated in Golgi-related trafficking pathways (Bergbrede et al., 2009; Valente et al., 2010; Chen et al., 2012). CAL reduces plasma membrane expression and recycling of  $\beta_1$ AR, and interferes with both  $\beta_1$ AR-mediated ERK signaling and postendocytotic receptor degradation via the lysosome (He et al., 2004; Koliwer et al., 2015). CAL overexpression retains SSTR5 in the Golgi apparatus, thereby reducing SSTR5 cell surface expression (Wente et al., 2005; Bauch et al., 2014). Additionally, CAL colocalizes with mGluR1a following agonist activation, and its overexpression decreases mGluR1a-stimulated ERK signaling (Zhang et al., 2008b). CAL is suggested to regulate mGluR5a function by increasing the expression of the receptor by a mechanism that involves the inhibition of mGluR5a ubiquitination (Cheng et al., 2010). Taken together, it appears CAL could have a regulatory role over the subcellular localization of a subset of GPCRs, perhaps by contributing to the post-translational modification of nascent and mature proteins that ultimately influence the sorting and trafficking fate.

### Additional GPCR-Interacting PDZ Proteins

**Spinophilin (Neurabin-2) and Neurabin-1.** Both spinophilin/neurabin-2 and neurabin-1 contain an amino-terminal actin-binding domain, a protein phosphatase 1 $\gamma$ -binding domain, a single PDZ domain, and a coiled-coil domain, with neurabin-1 also containing a carboxyl-terminal sterile alpha motif domain (Kelker et al., 2007) (Fig. 2). Spinophilin has been shown to interact with both D<sub>2</sub>R and  $\alpha_2$ -adrenergic receptor ( $\alpha_2$ AR) (Smith et al., 1999; Richman et al., 2001; Wang and Limbird, 2002; Brady et al., 2003; Wang et al., 2004). However, these interactions appear to be mediated by the third intracellular loop domains of these GPCRs, as opposed to interactions with PDZ-binding motifs. Spinophilin functions to promote membrane localization and inhibit the endocytosis and desensitization of  $\alpha_2$ ARs by competing for  $\beta$ -arrestin2 binding (Wang et al., 2004b). The interaction between spinophilin and  $\alpha_2$ AR is prevented by PKA-mediated phosphorylation of spinophilin, which results in increased agonist-stimulated  $\alpha_{2A}$ AR endocytosis (Xu et al., 2008).  $\beta_2$ AR activation also stimulates PKA-mediated spinophilin phosphorylation to increase  $\alpha_{2A}$ AR endocytosis (Cottingham et al., 2013). Conversely, spinophilin appears to promote RGS2-mediated inhibition of  $\alpha_2$ AR-evoked Ca<sup>2+</sup> signaling and RGS2-mediated modulation of  $\alpha_1$ -adrenergic receptor–NMDAR crosstalk (Wang et al., 2005; Liu et al., 2006). In spinophilin knockout mice, the  $\alpha_{2A}$ -adrenergic receptor ( $\alpha_{2A}$ AR) exhibits increased G protein coupling and sensitized responses to  $\alpha_{2A}$ AR agonists (Lu et al., 2010; Cottingham et al., 2012). Both spinophilin and neurabin-1 are implicated in the D<sub>1</sub>R-dependent regulation of AMPAR as well as long-term depression and potentiation, respectively (Allen et al., 2006). Spinophilin promotes prostacyclin receptor signaling via G $\alpha_s$  and influences both M1 muscarinic acetylcholine receptor and M3 muscarinic acetylcholine receptor (m3AChR) activity by enhancing RGS8-mediated inhibition of the G $\alpha_q$ -coupled signaling (Fujii et al., 2008; Kurogi et al., 2009; Ma et al., 2012). Similarly, spinophilin recruits RGS4 to m3AChR, and like RGS8, RGS4 antagonizes m3AChR inositol phosphate signaling (Ruiz de Azua et al., 2012). Spinophilin also

promotes  $\mu$ -opioid receptor ( $\mu$ OR)–mediated signaling via G $\alpha_i$ , but inhibits  $\mu$ OR-mediated ERK activation, while facilitating  $\mu$ OR endocytosis (Charlton et al., 2008; Fourla et al., 2012).

The interaction between spinophilin and opioid receptors appears to occur via the opioid receptor third intracellular loop and a conserved region of the carboxyl-termini, which is proximal to the seventh transmembrane domain (Fourla et al., 2012). Interestingly, this region appears to correlate with a small helical region identified in many class A rhodopsin-like GPCRs as helix 8 (Huynh et al., 2009). This domain is suggested to run perpendicular to the other seven helical transmembrane domains and is initiated by an *N-P-x-x-Y* motif (Huynh et al., 2009). In examining the amino acid sequences of class A rhodopsin-like GPCRs with this motif, a possible internal class I PDZ-binding motif, as characterized by an *S/T-x- $\varphi$*  motif, may be present near this region (Trejo, 2005). Furthermore, homologous regions are found within  $\alpha_2$ ARs and D<sub>2</sub>R, which also interact with spinophilin via the third intracellular loop domain. Notably, a recent study has identified helix 8 of D<sub>2</sub>R to associate with the PDZ domain of GIPC (Sensoy and Weinstein, 2015). Future studies could look to investigate whether secondary interactions with spinophilin may occur within the  $\alpha_2$ ARs and D<sub>2</sub>R carboxyl-terminal/helix 8, and whether these interactions require spinophilin's PDZ domain.

**SH3 and Multiple Ankyrin Repeat Domain Proteins.** SH3 and multiple ankyrin repeat domain (Shank) proteins are unified by the inclusion of multiple ankyrin repeat domains, an SH3 domain, a PDZ domain, and a sterile alpha motif domain; however, Shank2 lacks the ankyrin repeats (Fig. 2). Shank1B enhances mGluR1/5-mediated ERK1/2 and Ca<sup>2+</sup>-dependent signaling, and Shank3 is important for mGluR5-mediated ERK1/2 and cAMP response element-binding protein phosphorylation and subsequent mGluR5-mediated long-term depression (Sala et al., 2005; Verpelli et al., 2011). Furthermore, Shank3 prevents mGluR1-mediated inhibition of NMDAR via its association with Homer1A (Guo et al., 2004; Bertaso et al., 2010). Similarly, Shank1/3 modulates muscarinic acetylcholine receptor 1- and D<sub>2</sub>R-mediated inhibition of L-type Ca<sup>2+</sup> channels via Homer proteins (Olson et al., 2005). With regards to GPCR trafficking, Shank influences the clustering and subcellular localization of mGluR5 and calcium-independent  $\alpha$ -latrotoxin receptor C1RL/latrophilin 1 (Tu et al., 1999; Tobaben et al., 2000). Interestingly, a Shank/Homer1A complex can suppress NMDAR and AMPAR clustering and surface expression (Sala et al., 2003). Shank1 directly interacts with dynamin-2, which may provide insight into a mechanism of action in preventing GPCR-mediated crosstalk mechanisms and receptor surface expression (Okamoto et al., 2001). Future studies could look to investigate the role of Shank proteins in regulating GPCR trafficking and the crosstalk between GPCRs and ion channels.

**Partitioning Defective Proteins 3 and 6.** Partitioning defective (Par) proteins have been implicated in cellular polarization, and Par3 and Par6 are PDZ domain-containing members of the Par family (Fig. 2) (Macara, 2004). Par3 is implicated as having a role in synaptogenesis as a consequence of its interaction with BAI-1R (Duman et al., 2013). Additionally, Par3 has been shown to increase bradykinin receptor interactions with PLC $\beta$ 1 (Choi et al., 2010). Interestingly, both Par3 and Par6 interact and catalyze the activation of PLC $\beta$  downstream of heterotrimeric G proteins and form a complex with atypical PKCs (Joberty et al., 2000;

Cai et al., 2005). Taken together, these observations suggest that Par3 and Par6 may contribute to the regulation of GPCR-mediated  $G_{\alpha_q}$  signaling as well as feedback receptor desensitization by atypical PKCs.

**Multiple PDZ Protein 1.** Multiple PDZ protein 1 (MUPP1) is one of the largest PDZ domain-containing proteins and is comprised of an amino terminal L27 domain followed by 13 PDZ domains (Fig. 2). The interaction of MUPP1 with the melatonin 1 receptor facilitates melatonin 1 receptor  $G_{\alpha_i}$ -coupling, resulting in the inhibition of adenylyl cyclase activity (Guillaume et al., 2008). MUPP1 has also been shown to promote  $\gamma$ -aminobutyric acid B receptor-mediated  $Ca^{2+}$  signaling, although MUPP1 knockdown prolongs the decay of the odorant receptor olfactory receptor 2AG1-mediated  $Ca^{2+}$  response (Balasubramanian et al., 2007; Dooley et al., 2009). With regards to GPCR trafficking, MUPP1 increases the cell surface expression of 5-HT<sub>2A</sub>R (Jones et al., 2009). Additionally, MUPP1 promotes the targeting of SSTR3 to tight junctions, thereby influencing transepithelial permeability (Liew et al., 2009; Vockel et al., 2010). Given that MUPP1 influences NMDA-dependent AMPA trafficking and clustering, it is likely that MUPP1 also regulates the trafficking of GPCRs that encode PDZ-binding motifs, thereby contributing to GPCR-dependent regulation of synaptic activity (Krapivinsky et al., 2004).

**Tamalin (General Receptor for Phosphoinositides-Associated Scaffold Protein).** Tamalin or general receptor for phosphoinositides-associated scaffold protein encodes a PDZ domain, leucine zipper, and class I PDZ-binding motif on the distal carboxyl-terminal (Kitano et al., 2002, 2003) (Fig. 2). Tamalin promotes the plasma membrane localization of mGluR1a as well as the neuritic targeting of mGluR5 in hippocampal neurons (Kitano et al., 2002). Tamalin also interacts with mGluR2, mGluR3, and the  $\gamma$ -aminobutyric acid B2 receptor, but the functional consequence of these interactions remains to be determined (Kitano et al., 2002). In the absence of mGluRs or other potential GPCR binding partners, tamalin displays an autoinhibitory confirmation that is caused by the interaction between the tamalin PDZ domain and tamalin PDZ-binding motif (Sugi et al., 2007). Upon mGluR1a binding to the tamalin PDZ domain, the tamalin PDZ-binding motif is free to associate with MAGI-2 to further enhance the membrane localization of mGluR1a (Sugi et al., 2007). PDZ-guanine nucleotide exchange factor (GEF) 1/2 also contains PDZ-binding motifs, and future studies could look to determine whether they similarly exhibit autoregulation (Kuiperij et al., 2003, 2006; Ogawa et al., 2007).

**Neuronal Nitric Oxide Synthase.** Neuronal nitric oxide synthase (nNOS) contains an amino-terminal PDZ domain, a flavodoxin-like domain, and a flavin adenine dinucleotide-binding domain (Fig. 2). nNOS, in conjunction with RGS17, has been demonstrated to complex with multiple GPCRs, including  $\mu$ OR,  $\delta$  opioid receptor, serotonin 1A receptor, 5-HT<sub>2A</sub>R,  $\alpha_2$ AR, D<sub>1</sub>R, D<sub>2</sub>R, M2 muscarinic acetylcholine receptor, M4 muscarinic acetylcholine receptor, mGluR2, mGluR5, and cannabinoid receptor 1 (Sánchez-Blázquez et al., 2012). Activation of these receptors leads to the nNOS/NO-dependent recruitment of PKC $\gamma$  and Raf-1 to many of these GPCRs. nNOS also facilitates crosstalk between  $\mu$ OR and NMDAR (Rodríguez-Muñoz et al., 2008; Sánchez-Blázquez et al., 2010; Garzón et al., 2011). Interestingly, nNOS interacts with both PSD-95 and PSD-93, and is targeted to the neuromuscular junction via its interaction with PDZ protein  $\alpha$ -syntrophin (Brenman et al.,

1996; Adams et al., 2010). Although this nNOS interaction with PSD-95 is suggested to regulate NMDAR activity (Christopherson et al., 1999), it is yet to be determined whether these PDZ/PDZ protein interactions regulate GPCR function.

**Syntrophins.**  $\alpha$ -syntrophin,  $\beta_1$ -syntrophin, and  $\beta_2$ -syntrophin all have an amino-terminal pleckstrin-homology (PH) domain interrupted by a PDZ domain, followed by another PH domain and a syntrophin unique calmodulin-binding domain (Fig. 2) (Adams et al., 1995; Ahn et al., 1996; Chen et al., 2006). These syntrophins interact with  $\alpha_{1D}$ AR and collectively facilitate the functional expression of the receptor at the membrane, promoting  $\alpha_{1D}$ AR-mediated phosphatidylinositol hydrolysis, ERK1/2 phosphorylation, and  $Ca^{2+}$  mobilization (Chen et al., 2006; Lyssand et al., 2008, 2010, 2011). Neither  $\gamma_1$ -syntrophin nor  $\gamma_2$ -syntrophin comparably bind  $\alpha_{1D}$ AR, despite containing one PDZ domain and a PH domain, and their potential role in GPCR regulation remains uncertain (Chen et al., 2006).  $\alpha$ -syntrophin can additionally scaffold the PDZ protein nNOS and notably binds  $G\beta\gamma$  subunits via its PDZ domain (Brenman et al., 1996; Adams et al., 2010; Zhou et al., 2005).

**Protein Interacting with Protein Kinase C  $\alpha$  1.** The protein interacting with protein kinase C  $\alpha$  1 (PICK1) encodes one PDZ domain and an arfaptin homology domain/bin/amphiphysin/Rvs domain involved in cell membrane interactions (Katsushima et al., 2013) (Fig. 2). PICK1 promotes the intracellular clustering of the prolactin-releasing peptide receptor, influences plasma membrane expression of the growth hormone-releasing hormone receptor, and antagonizes growth hormone-releasing hormone receptor-mediated cAMP signaling (Lin et al., 2001; Katsushima et al., 2013). PICK1 regulates PKC phosphorylation of mGluR7a, regulates the presynaptic clustering of mGluR7, and mediates stable mGluR7 cell surface expression (Boudin et al., 2000; Dev et al., 2000; Suh et al., 2008). mGluR7a knock-in mice lacking a PDZ-binding motif exhibit deficits in hippocampal-dependent spatial memory and are highly susceptible to the convulsant drugs, and the disruption of the mGluR7a-PICK1 complex induces epilepsy-like seizures (Bertaso et al., 2008; Zhang et al., 2008a). Taken together, it appears PICK1 may be important for regulating the trafficking of a subset of GPCRs and may prove important in regulating GPCR-mediated signaling pathways. Notably, PICK1 can both homodimerize and heterodimerize with another PDZ domain-containing protein, syntenin-1 (Staudinger et al., 1997; Koroll et al., 2001).

**Syntenin-1.** Syntenin-1 contains two PDZ domains (Fig. 2) and has been found to self-associate as well as heterodimerize with PICK1 and form a complex with mGluR7 (Koroll et al., 2001; Hirbec et al., 2002; Enz and Croci, 2003). Although PICK1 regulates mGluR7 phosphorylation, clustering, and membrane expression, it is not yet clear what role syntenin-1 may play in this regulation (Boudin et al., 2000; Dev et al., 2000; Suh et al., 2008). Nonetheless, syntenin-1 has been demonstrated to enhance the membrane expression of G protein-coupled receptor 37 (endothelin receptor type B-like) (Dunham et al., 2009). In regards to signaling, syntenin-1 interacts with frizzled-7 and promotes c-Jun phosphorylation, CDC42 activation, and PKC $\alpha$  recruitment to the membrane (Luyten et al., 2008). Syntenin-1 can also heterodimerize with syntenin-2, although little is known about the role of syntenin-2 in GPCR regulation (Koroll et al., 2001).

**Sorting Nexin-27.** Sorting nexin-27 (SNX27) differs from other sorting nexins through the inclusion of an amino-terminal

PDZ domain, followed by a Phox homology domain and a Ras-associating domain (Fig. 2). SNX27 interacts with both serotonin 4A receptor and  $\beta_2$ AR in early endosome antigen 1-positive early endosomes (Joubert et al., 2004; Lauffer et al., 2010). Moreover, SNX27 is involved in regulating the recycling of  $\beta_2$ AR,  $\beta_1$ AR, and SSSTR5, thereby preventing receptor degradation (Lauffer et al., 2010; Temkin et al., 2011; Nakagawa and Asahi, 2013; Bauch et al., 2014). The regulation of  $\beta_2$ AR recycling by SNX27 is dependent upon Phox homology domain-mediated associations with the endosomal membrane (Lauffer et al., 2010). Furthermore, SNX27 interacts with the endosomal WASH complex to target  $\beta_2$ AR to the retromer tubule for efficient recycling (Temkin et al., 2011). Taken together, it appears SNX27 is capable of promoting the endosomal sorting and recycling of a subset of GPCRs, a role that may be generalizable to several other PDZ motif-encoding GPCRs.

**PDZ-GEFs (RAPGEFs, CNrasGEF, RA-GEF).** PDZ domain-containing GEFs (PDZ-GEF1 and PDZ-GEF2) share an approximately 56% sequence homology and include one or two cyclic nucleotide-binding domains, respectively, an N-terminal Ras GEF domain, a PDZ domain, a Ras-associating domain, and a Ras GEF catalytic domain within their molecular structure (Kuiperij et al., 2003, 2006) (Fig. 2). Similar to the PDZ domain-containing protein tamalin, PDZ-GEF1/2 have also been reported to contain a class I PDZ-binding motif at their carboxyl-termini, suggesting a capability for homo/heterooligomerization with PDZ domain-containing proteins or perhaps even autoregulatory capability via self-association (Kuiperij et al., 2003, 2006; Ogawa et al., 2007). Our current understanding of PDZ-GEF2 regulation of GPCRs is poor, but PDZ-GEF1 couples  $\beta_1$ AR to the activation of Ras (Pak et al., 2002). Furthermore, PDZ-GEF1 is essential for coupling the pituitary adenylate cyclase-activating polypeptide type I receptor to the ERK1/2 signaling pathway and the subsequent activation of neurogenesis, with no effect on cAMP accumulation (Emery et al., 2013).

**RGS Proteins with PDZ Domains (PDZ Domain-Containing RhoGEF, Leukemia-Associated RhoGEF, RGS3, and RGS12).** PDZ domain-containing RhoGEF (PDZ-RhoGEF) and leukemia-associated RhoGEF (LARG) are members of the RGS homology domain-containing RhoGEF subfamily and include an amino-terminal PDZ domain, an RGS-homology domain, a RhoGEF domain, and a PH domain (Fig. 2). LARG transduces  $G_{\alpha_{q/12/13}}$  activation into Rho activation via GPCRs, such as the Mas receptor, G2 accumulation receptor, muscarinic acetylcholine receptor 1, angiotensin II receptor 1, sphingosine-1 phosphate receptor 2, histamine H1 receptor, thromboxane A2 receptor, and endothelin 1 receptor (Booden et al., 2002; Ying et al., 2006; Medlin et al., 2010; Chiu et al., 2012; Pfreimer et al., 2012; Artamonov et al., 2013; Del Galdo et al., 2013). Similarly, PDZ-RhoGEF is proposed to contribute to gastrin-releasing peptide receptor-mediated activation of the Rho/ROCK pathway via  $G_{\alpha_{13}}$  (Patel et al., 2014). Finally, both PDZ-RhoGEF and LARG have been implicated in sustaining Rho activation following thrombin and lysophosphatidic acid receptor activation (Chikumi et al., 2002; Wang et al., 2004a; Yamada et al., 2005). Interestingly, both proteins appear capable of homo- and hetero-dimerization (Chikumi et al., 2004).

RGS12 contains one PDZ domain, a phosphotyrosine-binding domain, an RGS domain, two Ras-binding domains,

and a GoLoco motif (Fig. 2). The RGS12 PDZ domain binds to the interleukin-8 receptor B PDZ-binding motif, but the functional consequence of this interaction is not well defined (Snow et al., 1998). Notably, RGS12 has been suggested to couple  $D_2R$  to inward rectifier potassium channels Kir3.1/3.2 (Oxford and Webb, 2004). Regulator of G protein signaling 3 (RGS3) contains a membrane-targeting C2 domain, one PDZ domain, and an RGS domain (Fig. 2). RGS3 has been identified to inhibit  $G_{\alpha_q}$ - and  $G_{\alpha_i}$ -mediated signaling by acting as a GTPase-activating protein (Scheschonka et al., 2000). RGS3 antagonizes  $G_{\alpha_{q/11}}$  signaling via pheromone P factor receptor and muscarinic acetylcholine receptor 3 activation, and RGS3 promotes  $Ca^{2+}$  oscillatory behavior during submaximal muscarinic acetylcholine receptor 3 activation (Wang et al., 2002; Anger et al., 2004, 2007; Tovey and Willars, 2004; Ladds et al., 2007; Karakoula et al., 2008). RGS3 also antagonizes follicle-stimulating hormone receptor- and luteinizing hormone receptor-mediated inositol phosphate and cAMP accumulation (Castro-Fernandez et al., 2004). Furthermore, RGS3 has been demonstrated to suppress  $G_{\alpha_i}$ -mediated signaling pathways via  $\mu$ OR, muscarinic acetylcholine receptor 1, complement C5a receptor, and  $\beta_2$ AR, and even promote a  $G_{\alpha_s}$  bias for  $\beta_2$ AR (Potenza et al., 1999; Anger et al., 2007; Nishiura et al., 2009; Chakir et al., 2011). In contrast, RGS3 was shown to inhibit gonadotropin-releasing hormone receptor-stimulated inositol phosphate signaling via  $G_{\alpha_q}$ , but had no effect on cAMP signaling (Neill et al., 1997, 2001; Castro-Fernandez and Conn, 2002; Castro-Fernandez et al., 2002; Karakoula et al., 2008). Interestingly, RGS3 palmitoylation is increased following gonadotropin-releasing hormone receptor activation (Castro-Fernandez et al., 2002). Curiously, truncated RGS3 isoforms that have been reported to lack the amino-terminal and PDZ domain have also demonstrated a role in influencing GPCR activity, including sphingosine-1-phosphate receptors 1–3, angiotensin II receptor 1, endothelin 1 receptor, gonadotropin-releasing hormone receptor, serotonin 1A receptor, and muscarinic acetylcholine receptor 2/3 (Druey et al., 1996; Castro-Fernandez et al., 2003; Cho et al., 2003; Anger et al., 2004, 2007; Jaén and Doupnik, 2005). Distinguishing the role of LARG, PDZ-RhoGEF, RGS3, and RGS12 PDZ domain interactions, as opposed to RGS domain interactions with heterotrimeric G proteins, in the regulation of GPCR signaling remains a challenge.

## Role of PDZ Proteins in GPCR-Regulated Physiology

**PSD-95 Family of MAGUK PDZ Proteins.** The PDZ domain-containing MAGUK proteins play an essential role in human neurophysiology and development. This is demonstrated in mouse knockout studies, where PSD-95 and PSD-93 double-knockout mice exhibit severe deficiencies in AMPA currents, and SAP97 knockout mice show neonatal lethality (Caruana and Bernstein, 2001; Howard et al., 2010). Of particular interest is the observation that PSD-95 is essential for hallucinogenic and atypical antipsychotic actions of 5-HT<sub>2A</sub>R and 5-HT<sub>2C</sub>R (Abbas et al., 2009). In addition to being involved in atypical antipsychotic actions (Abbas et al., 2009), PDZ protein interactions with GPCRs also appear to be important in regulating stress and anxiety responses (Magalhaes et al., 2010). Preactivation of the CRFR1 receptor sensitizes 5-HT<sub>2A</sub>R-stimulated inositol phosphate formation,

which is dependent upon intact PDZ-binding motifs in both receptors, receptor endocytosis, and recycling (Magalhaes et al., 2010). Furthermore, the phenomenon can be blocked by a Tat-tagged fusion protein corresponding to the last 15 amino acids of the CRFR1 tail. In addition, pretreatment of mice with subthreshold doses of CRF into the prefrontal cortex sensitizes mouse anxiety responses to 2,5-dimethoxy-4-iodoamphetamine treatment (Magalhaes et al., 2010). Thus, it is possible that PDZ protein interactions may serve as a good pharmaceutical target for the treatment of disease.

SAP102 is important during early synaptic development, and SAP97 appears to be important in SSTR1-mediated growth cone dynamics, as evidenced by colocalization within the growth cone (Kim and Sheng, 2004; Elias et al., 2006; Cai et al., 2008). However, this role may not be limited to SAP97 and may include additional PDZ domain-containing proteins (Cai et al., 2008). PSD-95 plays a functional role in synaptic plasticity and contributes to GPCR-mediated regulation of both long-term potentiation and long-term depression (Xu, 2011). Notably, SAP97 also modulates the ability to regulate AMPA and NMDA receptors by promoting synaptic trafficking of these receptors (Howard et al., 2010). Acute overexpression of SAP97 in hippocampal slice cultures restored synaptic transmission in PSD-95/PSD-93 double knockout mice, and long-term overexpression of SAP97 throughout development led to enhancements in synaptic transmission in vivo (Howard et al., 2010). This regulation of NMDAR- and AMPAR-mediated synaptic transmission is likely to also involve a role of GPCRs. PSD-95 is reported to have an important role in regulating the trafficking dynamics of D<sub>1</sub>R in striatal neurons, and this regulatory role may contribute to L-adenosine triphosphate-induced dyskinesia (Porras et al., 2012). Thus, the role of PSD-95 in regulating D<sub>1</sub>R dynamics may be complicated by its ability to disrupt the formation of D<sub>1</sub>R/NMDAR complexes, a function that may be potentially directly associated with its role in the regulation of synaptic activity (Zhang et al., 2009). The association of PSD-95 with  $\beta_1$ AR allows it to form a complex with NMDAR, and this may contribute to the regulation of synaptic activity by adrenergic ligands (Hu et al., 2000).

**Other PDZ Proteins.** There are a number of other examples of PDZ proteins regulating GPCR-mediated regulation of physiologic functions. In the immune system, it has been found that the interaction of NHERF1 with the complement component C3a receptor is required for C3a-mediated mast cell degranulation, NF $\kappa$ B-activation, and chemokine production (Subramanian et al., 2012). CCR5 functions as a coreceptor for HIV-1 viral entry into mammalian cells by functioning as a cofactor for the entry of the virus (Henrich and Kuritzkes, 2013). NHERF1 interactions with CCR5 function to enhance actin filament rearrangement of host cells, a function that is essential to allow postcell entry HIV-1 replication (Hammad et al., 2010; Kuang et al., 2012). PDZK1 interactions with hIPR selectively facilitate hIPR-dependent activation of endothelial migration and vascular angiogenesis in vitro (Turner et al., 2011). MUPP1, the largest of the PDZ domain-containing adaptor proteins, promotes the targeting of SSTR3 to tight junctions and consequently influences transepithelial permeability of skin cells (Liew et al., 2009; Vockel et al., 2010). Tamalin plays an important role in regulating mGluR signaling, and tamalin knockout mice exhibit differences in their acute and adaptive responses

to morphine administration (Ogawa et al., 2007). Similarly, nNOS mediates a mechanism of crosstalk between  $\mu$ OR and NMDA receptors to regulate opioid tolerance and analgesia (Rodríguez-Muñoz et al., 2008; Sánchez-Blázquez et al., 2010; Garzón et al., 2011). PICK1 interactions with mGluR7a have been shown to be important for presynaptic mGluR7a clustering. mGluR7a knock-in mice lacking a PDZ-binding motif exhibit deficits in hippocampal-dependent spatial memory, and the disruption of the mGluR7a-PICK1 complex induces epileptic-like seizures (Boudin et al., 2000; Bertaso et al., 2008; Zhang et al., 2008a).  $\alpha$ -Syntrophin and  $\beta_2$ -syntrophin knockout mice display normal systolic blood pressure and resting heart rate; however, a double knockout prevents  $\alpha_{1D}$ AR-mediated blood pressure responses and exhibits a distinct hypotonic phenotype at rest, thereby demonstrating the capability for PDZ protein compensation in vivo (Lyssand et al., 2008).

## Concluding Remarks

GPCRs are influential in the regulation of every aspect of human physiology. Therefore, any advancement in the understanding of how they can be regulated could contribute to the design and development of new pharmacological treatment and prevention strategies for a multitude of human diseases (Bockaert et al., 2010; Heng et al., 2013). Accordingly, it is becoming clear that PDZ proteins play an important role in the regulation of GPCR signaling and trafficking. Considering it is estimated that 20% of GPCRs have PDZ-binding motifs and over 800 GPCRs have been identified in the human genome, it is safe to assume that this field is still in its infancy (Fredriksson et al., 2003; Lee and Zheng, 2010). Nevertheless, our growing understanding of the functional specificities and redundancies in PDZ regulation of GPCRs may lead to the development of new pharmacological compounds for precise modulation of GPCR activity. Such a strategy could be pertinent in the pharmacological treatment of a multitude of human pathologies, including, but not limited to, mental illnesses, cystic fibrosis, and osteoporosis (Abbas et al., 2009; Magalhaes et al., 2010; Mahon, 2012; Holcomb et al., 2014).

## Authorship Contributions

*Wrote or contributed to the writing of the manuscript:* Dunn, Ferguson.

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