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# Diacylglycerol, phosphatidic acid, and their metabolic enzymes in synaptic vesicle recycling

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## Abstract

The synaptic vesicle (SV) cycle includes exocytosis of vesicles loaded with a neurotransmitter such as glutamate, coordinated recovery of SVs by endocytosis, refilling of vesicles, and subsequent release of the refilled vesicles from the presynaptic bouton. SV exocytosis is tightly linked with endocytosis, and variations in the number of vesicles, and/or defects in the refilling of SVs, will affect the amount of neurotransmitter available for release (Sudhof, 2004). There is increasing interest in the roles synaptic vesicle lipids and lipid metabolizing enzymes play in this recycling. Initial emphasis was placed on the role of polyphosphoinositides in SV cycling as outlined in a number of reviews (Lim and Wenk, 2009; Martin, 2012; Puchkov and Haucke, 2013; Rohrbough and Broadie, 2005). Other lipids are now recognized to also play critical roles. For example, PLD1 (Humeau et al., 2001; Rohrbough and Broadie, 2005) and some DGKs (Miller et al., 1999; Nurrish et al., 1999) play roles in neurotransmission which is consistent with the critical roles for phosphatidic acid (PtdOH) and diacylglycerol (DAG) in the regulation of SV exo/endocytosis (Cremona et al., 1999; Exton, 1994; Huttner and Schmidt, 2000; Lim and Wenk, 2009; Puchkov and Haucke, 2013; Rohrbough and Broadie, 2005). PLD generates phosphatidic acid by catalyzing the hydrolysis of phosphatidylcholine (PtdCho) and in some systems this PtdOH is dephosphorylated to generate DAG. In contrast, DGK catalyzes the phosphorylation of DAG thereby converting it into PtdOH. While both enzymes are poised to regulate the levels of DAG and PtdOH, therefore, they both lead to the generation of PtdOH and could have opposite effects on DAG levels. This is particularly important for SV cycling as PtdOH and DAG are both needed for evoked exocytosis (Lim and Wenk, 2009; Puchkov and Haucke, 2013; Rohrbough and Broadie, 2005). Two lipids and their involved metabolic enzymes, two sphingolipids have also been implicated in exocytosis: sphingosine (Camoletto et al., 2009; Chan et al., 2012; Chan and Sieburth, 2012; Darios et al., 2009; Kanno et al., 2010; Rohrbough et al., 2004) and sphingosine-1-phosphate (Chan, Hu, 2012; Chan and Sieburth, 2012; Kanno et al., 2010). Finally a number of reports have focused on the somewhat less well studies roles of sphingolipids and cholesterol in SV cycling. In this report, we review the recent understanding of the roles PLDs, DGKs, and DAG lipases, as well as sphingolipids and cholesterol play in synaptic vesicle cycling.

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**Keywords**

Synaptic vesicle cycle; Neuroscience; phosphatidic acid; Diacylglycerol; Diacylglycerol kinase; Sphingosine; Phospholipase D; Cholesterol

## Phosphatidylcholine-specific phospholipases D1 and D2

PLDs1 and 2 have been implicated in the release of neurotransmitter release. Most of the available data pertains to the role PLD1 plays in this process ((Humeau et al., 2001; Rohrbough and Broadie, 2005) and see (Almena and Merida, 2011; Kanoh et al., 2002; Merida et al., 2008; van Blitterswijk and Houssa, 2000)). Using dominant-negative constructs of PLD1 and PD2, Humeau et al. provided strong evidence for a role for PLD1, but not PLD2, in neurotransmitter release from *Aplysia californica* neurons (Humeau et al., 2001) substantiating other studies implicating PLD1 in the CNS (Humeau et al., 2001; Rohrbough and Broadie, 2005; Sun et al., 2013). Consistent with these observations, PLD1 is largely localized in neurons (Humeau et al., 2001; Klein, 2005; Rohrbough and Broadie, 2005; Zhang et al., 2004) but is also present in oligodendrites, while PLD2 is largely found in astrocytes (e.g. see (Kim et al., 2010b; Zhang et al., 2004)). While PLD1 seems to be involved in exocytosis (Humeau et al., 2001; Vitale et al., 2001), PLD2 has been implicated in the modulation of glutamate transporter function (Mateos et al., 2012) and the internalization of mGluR (Bhattacharya et al., 2004). Interestingly, PLD2 ablation has been shown to alleviate the synaptic dysfunction linked to Alzheimer's disease (Oliveira et al., 2010; Oliveira and Di Paolo, 2010). Using brain slices, these studies indicate that oligomeric Aβ does not suppress longterm potentiation in PLD2 deficiency in the hippocampus implicating PLD2 in the synaptotoxic action of Aβ. A particularly interesting aspect of this work was the observation that ablation of PLD2 rescues memory deficits and leads to synaptic protection in a transgenic mouse model of AD (SwAPP) even in the presence of an Aβ over-load (Oliveira et al., 2010). In addition to these studies, PLD2 has been implicated in glutamate transport (Mateos et al., 2012). These studies may increase the interest in the roles of this PLD isoform in the CNS.

PLDs catalyze the hydrolysis of phosphatidylcholine leading to the production of PtdOH. Consistent with a PLD role in neurotransmitter release, this lipid has been show to modulate a number of proteins involved in exocytosis. For example, PtdOH directly binds to some small GTPase, as well as proteins involved in vesicular trafficking such as NSF and syntaxin-1A (Jang et al., 2012). This lipid also affects exocytosis indirectly via the activation of phosphatidylinositol-4-phosphate 5-kinase, which catalyzes the production of PtdIns(4,5)$P_2$ (Honda et al., 1999). Some of the strongest evidence for a PtdOH role in SV cycling derives from in vitro reconstituted assays involving a liposomal flotation assay for fusion with purified yeast vacuolar SNARE chaperones Sec17p/Sec18p, and the multifunctional HOPS complex with the Sec1-Munc18 family. In this assay, PtdOH was one of the lipids shown to be critical for SNARE complex assembly and for fusion (Mima and Wickner, 2009). Finally given the potential role of PLD2 in glutamate transport (Mateos et al., 2012), it is interesting to note that this lipid has been shown to modulate ion channels/

transporters in plants (Liu et al., 2013; Yu et al., 2010) and providing support to the speculation that it's involved in modulating a glutamate transporter.

## Diacylglycerol and related enzymes: diacylglycerol kinase, diacylglycerol lipase

DAG has also been implicated in SV cycling (Cremona et al., 1999; Huttner and Schmidt, 2000; Lim and Wenk, 2009; Rohrbough and Broadie, 2005; Vijayakrishnan and Broadie, 2006; Wenk, 2005). The role of this lipid, however, appears to be more confined to the regulation of two proteins critical to synaptic vesicle cycling: munc13-1/2 and PKC (Basu et al., 2007; Kazanietz, 2000, 2002; Merida et al., 2008; Villar et al., 2001; Xue et al., 2009). The involvement of PKC is a bit controversial. Xue et al. showed that expression of a dominant-negative PKCα prevents the phorbol-ester facilitation of exocytosis in PC12 cells. Using hippocampal neurons isolated from munc13-1/munc13-2 deficient mice, however, Rhee et al. showed that this protein family and not PKC are necessary for evoked exocytosis (Rhee et al., 2002). Further, expression of a DAG-binding defective these neurons showed the DAG binding domain was essential for the evoked release of neurotransmitter. While the precise role of a PKC or munc13 may be cell type or system dependent, it is clear that DAG plays a central role in modulating neurotransmitter release.

One of the key enzymes involved in modulating DAG levels are the DGKs. The physiological roles of mammalian DGKs in the CNS are also now starting to emerge, and specific functions have been identified for several neuronal isoforms (Goto and Kondo, 1999a; Goto et al., 2014; Hozumi and Goto, 2012; Ishisaka and Hara, 2014; Tu-Sekine and Raben, 2011) including DGK-ε (Musto and Bazan, 2006; Rodriguez de Turco et al., 2001); DGK-ζ and DGK-β (Kim et al., 2010a; Shirai et al., 2010); and DGK-ι (Seo et al., 2010). DGK-α, while present in the CNS, is largely confined to glial cells (Goto and Kondo, 1999b). DGK-β probably does not play a role in synaptic vesicle recycling but is involved in branching and spine formation (Hozumi et al., 2009; Shirai et al., 2010). Perhaps the most compelling evidence for this is the data from primary cultured hippocampal neurons isolated from DGK-β KO mice where branching and spine formation were decreased and this phenotype was rescued by expression of wild type DGK-β (Hozumi et al., 2009). Although these data don't directly address a role for DGK-β in synaptic vesicle recycling, there is evidence that this isoform plays a role in hyperactivity disorder and bipolar disease (Caricasole et al., 2001; Ishisaka et al., 2012). DGK-ζ, similar to DGK-β plays a role in spine density as well but this isoform appears to promote spine maintenance and is largely a postsynaptic process (Kim et al., 2009). DGK-ε likely modulates neuronal synaptic activity, neuronal plasticity, and epileptogenesis (Musto and Bazan, 2006; Rodriguez de Turco et al., 2001), although the mechanism is not clear. Targeted ablation of DGK-ε in mice led to an increased resistance to electro-convulsive shock with shorter tonic seizures and faster recovery than their wild type counterparts.

Two DGK isoforms that are more strongly associated with synaptic transmission are DGK-ι and DGK-θ. Using mice in which DGK-i was knocked out, Yang et al. showed that this isoform may be involved in regulating presynaptic glutamate release during DHPG (3,5-dihydroxyphenylglycine)-induced long-term potentiation (Yang et al., 2010). While DGK-θ

is predominantly expressed in the CNS (Tu-Sekine and Raben, 2011), the primary evidence for function in neurotransmitter release stems from work on the *Caenorhabditis elegans* homolog of DGK-θ, DGK-1. Knock-out animals (*dgk-1*$^{-/-}$) exhibit a constitutive increase in acetylcholine release due to hyper-stimulation of the DAG-dependent vesicle-priming protein unc-13 ((Miller et al., 1999; Nurrish et al., 1999) and see (Kanoh et al., 2002; Merida et al., 2008)). A role for this enzyme in synaptic vesicle cycling in mammalian neurons has not yet been established.

DAG lipase (DAGL) is an enzyme that catalyzes the hydrolysis of DAG yielding a free fatty acid and 2-monoacylglycerol. Two genes have been identified for two different isozymes designated DAGL-a and DAGL-b. In neurons, these enzymes are predominately post-synaptic and have largely been implicated in the production and function of endocannabinoids and arachidonic acid in the brain ((Uchigashima et al., 2007; Yoshida et al., 2006) and see (Garcia del Cano et al., 2014; Reisenberg et al., 2012)). Evidence that they are involved in modulating neurotransmitter release is lacking.

## DAG and PtdOH in membrane fusion

The question that often arises pertains to how DAG and PtdOH mediate exocytosis or endocytosis. Clearly, the above discussion indicates that a large part of the mechanism involves their interaction, thereby affecting localization and/or activation, of proteins involved in these processes. In addition to this, these two lipids are often considered to be fusogenic. This refers to the notion that these lipids support, and may even accelerate, the fusion of membrane bilayers. This is partly due to the fact that both PtdOH and DAG are cone shaped lipids and promote negative curvature. In that, increases in these lipids on the inner leafiet of the synaptic membrane, and possibly the outer leafiet of the synaptic vesicle, would enhance membrane fusion (Chasserot-Golaz et al., 2010; Chernomordik and Kozlov, 2005). It's interesting to speculate that the generation and inter-conversion of these lipids could provide a unique opportunity for regulating the presence of fusogenic lipids with the recruitment and/or activation of specific proteins involved in exo/endocytosis.

## The sphingolipids

There is increasing evidence to support a role for sphingolipids in neurotransmitter release ((Colombaioni and Garcia-Gil, 2004) and see (Brailoiu et al., 2002; Camoletto et al., 2009; Darios et al., 2009; Kanno et al., 2010)). Sphingosine was shown to activate the synaptic vesicle protein synapto-brevin leading to SNARE complex formation which is involved in membrane fusion. In support of this, exocytosis was increased in response to sphingosine in isolated nerve terminals, neuromuscular junctions, neuroendocrine cells and hippocampal neurons, in a synaptobrevin-2-dependent manner (Darios et al., 2009). In an exciting recent study from de Camilli's group, they showed that knockdown of sphingosine kinases leads to an endocytic recycling defect. Further, while wild type C. elegans sphingosine kinase rescues the phenotype, a mutation that disrupts the hydrophobic patch of this enzyme is unable to rescue the loss-of-function mutations of this kinase (Shen et al., 2014).

## Cholesterol

The role of cholesterol in the SV cycle has been less studied and confusion still exists. Some studies have shown that cholesterol depletion by methyl-b-cyclodextrin leads to a suppression of exocytosis (Belmonte et al., 2005; Chamberlain et al., 2001; Churchward et al., 2005). This may be due to an indirect effect involving a suppression of evoked calcium release or the result of membrane alterations including sequestration of components in specific lipid domains. Other studies have shown that cholesterol plays an important role in synaptic vesicle cycling. For example, cholesterol has been shown to bind synaptophysin and modulate exocytosis but not endocytosis in PC12 cells (Thiele et al., 2000). In the de Camilli study noted above, these investigators showed that altering the cholesterol/sphingomyelin ratio in the plasma membrane is important for proper targeting of sphingosine kinase to active zones in neurons (Shen et al., 2014).

## Summation

Identifying the roles of various lipids in the modulation of neurotransmitter release is an reinvigorated field that promises to yield exciting results. In addition to expanding the roles identified above, our understanding of the roles of the particular lipid species as well as the chemistry and biophysical properties of the lipids and membranes in which they reside will lead to exciting discoveries. These studies will not only expand our fundamental knowledge of lipids in neuroscience, they promise to provide new therapeutic insights. It seems we're on the cusp of a very exciting time in lipid research.

## References

Almena M, Merida I. Shaping up the membrane: diacylglycerol coordinates spatial orientation of signaling. Trends Biochem Sci. 2011; 36:593–603. [PubMed: 21798744]

Basu J, Betz A, Brose N, Rosenmund C. Munc13-1 C1 domain activation lowers the energy barrier for synaptic vesicle fusion. J Neurosci: Off J Soc Neurosci. 2007; 27:1200–10.

Belmonte SA, Lopez CI, Roggero CM, De Blas GA, Tomes CN, Mayorga LS. Cholesterol content regulates acrosomal exocytosis by enhancing Rab3A plasma membrane association. Dev Biol. 2005; 285:393–408. [PubMed: 16099449]

Bhattacharya M, Babwah AV, Godin C, Anborgh PH, Dale LB, Poulter MO, et al. Ral and phospholipase D2-dependent pathway for constitutive metabotropic glutamate receptor endocytosis. J Neurosci: Off J Soc Neurosci. 2004; 24:8752–61.

Brailoiu E, Cooper RL, Dun NJ. Sphingosine 1-phosphate enhances spontaneous transmitter release at the frog neuromuscular junction. Br J Pharmacol. 2002; 136:1093–7. [PubMed: 12163341]

Camoletto PG, Vara H, Morando L, Connell E, Marletto FP, Giustetto M, et al. Synaptic vesicle docking: sphingosine regulates syntaxin1 interaction with Munc18. PloS One. 2009; 4:e5310. [PubMed: 19390577]

Caricasole A, Bettini E, Sala C, Roncarati R, Kobayashi N, Caldara F, et al. Molecular cloning and characterization of the human diacylglycerol kinase beta (DGK{beta}) gene: alternative splicing generates DGK{beta} isotypes with different properties. J Biol Chem. 2001; 277(7):4790e6. [PubMed: 11719522]

Chamberlain LH, Burgoyne RD, Gould GW. SNARE proteins are highly enriched in lipid rafts in PC12 cells: implications for the spatial control of exocytosis. Proc Natl Acad Sci U S A. 2001; 98:5619–24. [PubMed: 11331757]

Chan JP, Hu Z, Sieburth D. Recruitment of sphingosine kinase to presynaptic terminals by a conserved muscarinic signaling pathway promotes neurotransmitter release. Genes Dev. 2012; 26:1070–85. [PubMed: 22588719]

Chan JP, Sieburth D. Localized sphingolipid signaling at presynaptic terminals is regulated by calcium influx and promotes recruitment of priming factors. J Neurosci: Off J Soc Neurosci. 2012; 32:17909–20.

Chasserot-Golaz S, Coorssen JR, Meunier FA, Vitale N. Lipid dynamics in exocytosis. Cell Mol Neurobiol. 2010; 30:1335–42. [PubMed: 21080057]

Chernomordik LV, Kozlov MM. Membrane hemifusion: crossing a chasm in two leaps. Cell. 2005; 123:375–82. [PubMed: 16269330]

Churchward MA, Rogasevskaia T, Hofgen J, Bau J, Coorssen JR. Cholesterol facilitates the native mechanism of $Ca^{2+}$-triggered membrane fusion. J Cell Sci. 2005; 118:4833–48. [PubMed: 16219690]

Colombaioni L, Garcia-Gil M. Sphingolipid metabolites in neural signalling and function. Brain Res Rev. 2004; 46:328–55. [PubMed: 15571774]

Cremona O, Di PG, Wenk MR, Luthi A, Kim WT, Takei K, et al. Essential role of phosphoinositide metabolism in synaptic vesicle recycling. Cell. 1999; 99:179–88. [PubMed: 10535736]

Darios F, Wasser C, Shakirzyanova A, Giniatullin A, Goodman K, Munoz-Bravo JL, et al. Sphingosine facilitates SNARE complex assembly and activates synaptic vesicle exocytosis. Neuron. 2009; 62:683–94. [PubMed: 19524527]

Exton JH. Phosphatidylcholine breakdown and signal transduction. [Review] Biochim Biophys Acta. 1994; 1212:26–42. [PubMed: 8155724]

Garcia del Cano G, Montana M, Aretxabala X, Gonzalez-Burguera I, Lopez de Jesus M, Barrondo S, et al. Nuclear phospholipase C-beta1 and diacylglycerol LIPASE-alpha in brain cortical neurons. Adv Biol Regul. 2014; 54:12–23. [PubMed: 24076015]

Goto K, Kondo H. Diacylglycerol kinase in the central nervous systememolecular heterogeneity and gene expression. Chem Phys Lipids. 1999a; 98:109e17. [PubMed: 10358933]

Goto K, Kondo H. Diacylglycerol kinase: molecular diversity and gene expression in central nervous system. Tanpakushitsu Kakusan Koso. 1999b; 44:976e82. [PubMed: 10396972]

Goto K, Tanaka T, Nakano T, Okada M, Hozumi Y, Topham MK, et al. DGKzeta under stress conditions: “to be nuclear or cyto-plasmic, that is the question”. Adv Biol Regul. 2014; 54:242–53. [PubMed: 24119575]

Honda A, Nogami M, Yokozeki T, Yamazaki M, Nakamura H, Watanabe H, et al. Phosphatidylinositol 4-phosphate 5-kinase alpha is a downstream effector of the small G protein ARF6 in membrane ruffle formation. [In Process Citation] Cell. 1999; 99:521e32.

Hozumi Y, Goto K. Diacylglycerol kinase beta in neurons: functional implications at the synapse and in disease. Adv Biol Regul. 2012; 52:315–25. [PubMed: 22781745]

Hozumi Y, Watanabe M, Otani K, Goto K. Diacylglycerol kinase beta promotes dendritic outgrowth and spine maturation in developing hippocampal neurons. BMC Neurosci. 2009; 10(99)

Humeau Y, Vitale N, Chasserot-Golaz S, Dupont JL, Du G, Frohman MA, et al. A role for phospholipase D1 in neurotransmitter release. Proc Natl Acad Sci U S A. 2001; 98:15300–5. [PubMed: 11752468]

Huttner WB, Schmidt A. Lipids, lipid modification and lipid-protein interaction in membrane budding and fissione-insights from the roles of endophilin A1 and synaptophysin in synaptic vesicle endocytosis. Curr Opin Neurobiol. 2000; 10:543–51. [PubMed: 11084315]

Ishisaka M, Hara H. The roles of diacylglycerol kinases in the central nervous system: review of genetic studies in mice. J Pharmacol Sci. 2014; 124:336–43. [PubMed: 24599142]

Ishisaka M, Kakefuda K, Oyagi A, Ono Y, Tsuruma K, Shimazawa M, et al. Diacylglycerol kinase beta knockout mice exhibit attention-deficit behavior and an abnormal response on methylphenidate-induced hyperactivity. PloS One. 2012; 7:e37058. [PubMed: 22590645]

Jang JH, Lee CS, Hwang D, Ryu SH. Understanding of the roles of phospholipase D and phosphatidic acid through their binding partners. Prog Lipid Res. 2012; 51:71–81. [PubMed: 22212660]

Kanno T, Nishizaki T, Proia RL, Kajimoto T, Jahangeer S, Okada T, et al. Regulation of synaptic strength by sphingosine 1-phosphate in the hippocampus. Neuroscience. 2010; 171:973–80. [PubMed: 20950672]

Kanoh H, Yamada K, Sakane F. Diacylglycerol kinases: emerging downstream regulators in cell signaling systems. J Biochem (Tokyo). 2002; 131:629–33. [PubMed: 11983067]

Kazanietz MG. Protein kinase C and novel receptors for the phorbol esters and the second messenger diacylglycerol. Med (B Aires). 2000; 60:685–8.

Kazanietz MG. Novel “nonkinase” phorbol ester receptors: the C1 domain connection. Mol Pharmacol. 2002; 61:759–67. [PubMed: 11901214]

Kim K, Yang J, Kim E. Diacylglycerol kinases in the regulation of dendritic spines. J Neurochem. 2010a; 112:577–87. [PubMed: 19922438]

Kim K, Yang J, Zhong XP, Kim MH, Kim YS, Lee HW, et al. Synaptic removal of diacylglycerol by DGKzeta and PSD-95 regulates dendritic spine maintenance. EMBO J. 2009; 28:1170–9. [PubMed: 19229292]

Kim M, Moon C, Kim H, Shin MK, Min do S, Shin T. Developmental levels of phospholipase D isozymes in the brain of developing rats. Acta Histochem. 2010b; 112:81e91. [PubMed: 19010519]

Klein J. Functions and pathophysiological roles of phospholipase D in the brain. J Neurochem. 2005; 94:1473–87. [PubMed: 16042758]

Lim, L.; Wenk, M. Neuronal membrane lipids-their role in the synaptic vesicle cycle. In: Lajtha, A.; Tettamanti, G.; Goracci, G., editors. Handbook of neurochemistry and molecular neurobiology; neural lipids. 3rd. Springer; 2009. p. 223e38

Liu Y, Su Y, Wang X. Phosphatidic acid-mediated signaling. Adv Exp Med Biol. 2013; 991:159–76. [PubMed: 23775695]

Martin TF. Role of PI(4,5)P(2) in vesicle exocytosis and membrane fusion. Sub-cellular Biochem. 2012; 59:111–30.

Mateos MV, Giusto NM, Salvador GA. Distinctive roles of PLD signaling elicited by oxidative stress in synaptic endings from adult and aged rats. Biochim Biophys Acta. 2012; 1823:2136–48. [PubMed: 23010583]

Merida I, Avila-Flores A, Merino E. Diacylglycerol kinases: at the hub of cell signalling. Biochem J. 2008; 409:1–18. [PubMed: 18062770]

Miller KG, Emerson MD, Rand JB. Goalpha and diacylglycerol kinase negatively regulate the Gqalpha pathway in C. elegans [see comments] Neuron. 1999; 24:323–33. [PubMed: 10571227]

Mima J, Wickner W. Complex lipid requirements for SNARE- and SNARE chaperone-dependent membrane fusion. J Biol Chem. 2009; 284:27114–22. [PubMed: 19654322]

Musto A, Bazan NG. Diacylglycerol kinase epsilon modulates rapid kindling epileptogenesis. Epilepsia. 2006; 47:267–76. [PubMed: 16499750]

Nurrish S, Segalat L, Kaplan JM. Serotonin inhibition of synaptic transmission: Galpha(0) decreases the abundance of UNC-13 at release sites. Neuron. 1999; 24:231–42. [PubMed: 10677040]

Oliveira TG, Chan RB, Tian H, Laredo M, Shui G, Staniszewski A, et al. Phospholipase d2 ablation ameliorates Alzheimer's disease-linked synaptic dysfunction and cognitive deficits. J Neurosci: Off J Soc Neurosci. 2010; 30:16419–28.

Oliveira TG, Di Paolo G. Phospholipase D in brain function and Alzheimer's disease. Biochim Biophys Acta. 2010; 1801:799–805. [PubMed: 20399893]

Puchkov D, Haucke V. Greasing the synaptic vesicle cycle by membrane lipids. Trends cell Biol. 2013; 23:493–503. [PubMed: 23756446]

Reisenberg M, Singh PK, Williams G, Doherty P. The diacylglycerol lipases: structure, regulation and roles in and beyond endocannabinoid signalling. Philos Trans R Soc Lond Ser B Biol Sci. 2012; 367:3264–75. [PubMed: 23108545]

Rhee JS, Betz A, Pyott S, Reim K, Varoqueaux F, Augustin I, et al. Beta phorbol ester- and diacylglycerol-induced augmentation of transmitter release is mediated by Munc13s and not by PKCs. Cell. 2002; 108:121–33. [PubMed: 11792326]

Rodriguez de Turco EB, Tang W, Topham MK, Sakane F, Marcheselli VL, Chen C, et al. Diacylglycerol kinase epsilon regulates seizure susceptibility and long-term potentiation through arachidonoylinositol lipid signaling. Proc Natl Acad Sci U S A. 2001; 98:4740–5. [PubMed: 11287665]

Rohrbough J, Broadie K. Lipid regulation of the synaptic vesicle cycle. Nat Rev Neurosci. 2005; 6:139–50. [PubMed: 15685219]

Rohrbough J, Rushton E, Palanker L, Woodruff E, Matthies HJ, Acharya U, et al. Ceramidase regulates synaptic vesicle exocytosis and trafficking. J Neurosci: Off J Soc Neurosci. 2004; 24:7789–803.

Seo J, Kim K, Jang S, Han S, Choi SY, Kim E. Regulation of hippocampal long-term potentiation and long-term depression by diacylglycerol kinasezeta. Hippocampus. 2012; 22(5):1018e26. [PubMed: 21069783]

Shen H, Giordano F, Wu Y, Chan J, Zhu C, Milosevic I, et al. Coupling between endocytosis and sphingosine kinase 1 recruitment. Nat Cell Biol. 2014; 16(7):652e62. [PubMed: 24929359]

Shirai Y, Kouzuki T, Kakefuda K, Moriguchi S, Oyagi A, Horie K, et al. Essential role of neuron-enriched diacylglycerol kinase (DGK), DGKbeta in neurite spine formation, contributing to cognitive function. PLoS One. 2010; 5:e11602. [PubMed: 20657643]

Sudhof TC. The synaptic vesicle cycle. Annu Rev Neurosci. 2004; 27:509–47. [PubMed: 15217342]

Sun L, Gooding HL, Brunton PJ, Russell JA, Mitchell R, Fleetwood-Walker S. Phospholipase D-mediated hypersensitivity at central synapses is associated with abnormal behaviours and pain sensitivity in rats exposed to prenatal stress. Int J Biochem Cell Biol. 2013; 45:2706–12. [PubMed: 23932932]

Thiele C, Hannah MJ, Fahrenholz F, Huttner WB. Cholesterol binds to synaptophysin and is required for biogenesis of synaptic vesicles. Nat Cell Biol. 2000; 2:42–9. [PubMed: 10620806]

Tu-Sekine B, Raben DM. Regulation and roles of neuronal diacylglycerol kinases: a lipid perspective. Crit Rev Biochem Mol Biol. 2011; 46:353–64. [PubMed: 21539478]

Uchigashima M, Narushima M, Fukaya M, Katona I, Kano M, Watanabe M. Subcellular arrangement of molecules for 2-arachidonoyl-glycerol-mediated retrograde signaling and its physiological contribution to synaptic modulation in the striatum. J Neurosci. 2007; 27:3663–76. [PubMed: 17409230]

van Blitterswijk WJ, Houssa B. Properties and functions of diacylglycerol kinases. Cell Signal. 2000; 12:595–605. [PubMed: 11080611]

Vijayakrishnan N, Broadie K. Temperature-sensitive paralytic mutants: insights into the synaptic vesicle cycle. Biochem Soc Trans. 2006; 34:81–7. [PubMed: 16417488]

Villar AV, Goni FM, Alonso A. Diacylglycerol effects on phosphatidylinositol-specific phospholipase C activity and vesicle fusion. FEBS Lett. 2001; 494:117–20. [PubMed: 11297746]

Vitale N, Caumont AS, Chasserot-Golaz S, Du G, Wu S, Sciorra VA, et al. Phospholipase D1: a key factor for the exocytotic machinery in neuroendocrine cells. EMBO J. 2001; 20:2424–34. [PubMed: 11350931]

Wenk MR. The emerging field of lipidomics. Nat Rev Drug Discov. 2005; 4:594–610. [PubMed: 16052242]

Xue R, Zhao Y, Chen P. Involvement of PKC alpha in PMA-induced facilitation of exocytosis and vesicle fusion in PC12 cells. Biochem Biophys Res Commun. 2009; 380:371–6. [PubMed: 19250646]

Yang J, Seo J, Nair R, Han S, Jang S, Kim K, et al. DGKiota regulates presynaptic release during mGluR-dependent LTD. EMBO J. 2010; 30:165–80. [PubMed: 21119615]

Yoshida T, Fukaya M, Uchigashima M, Miura E, Kamiya H, Kano M, et al. Localization of diacylglycerol lipase-alpha around postsynaptic spine suggests close proximity between production site of an endocannabinoid, 2-arachidonoyl-glycerol, and presynaptic cannabinoid CB1 receptor. J Neurosci. 2006; 26:4740–51. [PubMed: 16672646]

Yu L, Nie J, Cao C, Jin Y, Yan M, Wang F, et al. Phosphatidic acid mediates salt stress response by regulation of MPK6 in Arabidopsis thaliana. New Phytol. 2010; 188:762–73. [PubMed: 20796215]

Zhang Y, Huang P, Du G, Kanaho Y, Frohman MA, Tsirka SE. Increased expression of two phospholipase D isoforms during experimentally induced hippocampal mossy fiber outgrowth. Glia. 2004; 46:74–83. [PubMed: 14999815]