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

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A B S T R A C T

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

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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.

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 long-term 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.