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Primary phospholipase C and brain disorders

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ABSTRACT

In the brain, the primary phospholipase C (PLC) proteins, PLCβ, and PLCγ, are activated primarily by neurotransmitters, neurotrophic factors, and hormones through G protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs). Among the primary PLC isozymes, PLCβ1, PLCβ4, and PLCγ1 are highly expressed and differentially distributed, suggesting a specific role for each PLC subtype in different regions of the brain. Primary PLCs control neuronal activity, which is important for synapse function and development. In addition, dysregulation of primary PLC signaling is linked to several brain disorders including epilepsy, schizophrenia, bipolar disorder, Huntington's disease, depression and Alzheimer's disease. In this review, we included current knowledge regarding the roles of primary PLC isozymes in brain disorders.

1. Introduction

Neuronal activity affects gene transcription and local protein synthesis of synaptic molecules, which ultimately regulates synaptic function and development in the brain. Neuronal activity-dependent release of large numbers of extracellular ligands (e.g., neurotransmitters, neurotrophic factors, and hormones) affects neuronal development, synapse function, and neurological disorders (Flavell and Greenberg, 2008). These extracellular ligands activate the primary phospholipase C (PLC) isozymes, PLCβ (1–4) and PLCγ (1 and 2), through G protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs) (Follo et al., 2015; Yang et al., 2013). Activation of PLCβ or PLCγ cleaves phosphatidylinositol 4,5-bisphosphate (PIP2) into the second messengers, diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3), which play key roles in intracellular signal transduction. Although PLCβ and PLCγ isozymes have similar catalytic functions, several studies have reported their ability to play strikingly different roles in the brain. PLCβ1 is detected at high levels within several regions of the brain including the cerebral cortex, hippocampus, amygdala, lateral septum, and the olfactory bulb (Ross et al., 1989). Disruption of PLCβ1-mediated signaling in the brain is associated with epilepsy, schizophrenia, and bipolar disorder (Garcia del Cano et al., 2014; Kim et al., 1997; Kurian et al., 2010; Lo Vasco et al., 2013; Poduri et al., 2012). PLCβ4 is expressed at high levels in the retina cerebellum, but is rarely detected in the forebrain (Tanaka and Kondo, 1994). The expression patterns of PLCβ4 reflect its functional roles, with dysfunction of PLCβ4 linked to ataxia, absence seizures, and visual processing defects (Cheong

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et al., 2009; Jiang et al., 1996; Kim et al., 1997). Furthermore, abnormal expression of PLCβ4 was observed in individuals with Huntington's disease (Marchina et al., 2014). PLCγ1 is expressed in the forebrain, specifically in the cortex and hippocampus (Jang et al., 2013; Suh et al., 2008). Genetic studies suggest that PLCγ1 is involved in the development of several brain disorders including epilepsy, bipolar disorder, Huntington's disease, and depression (Giralt et al., 2009; He et al., 2010; Rantamaki et al., 2007; Turecki et al., 1998). In this review, we discuss the potential roles of PLCβ1, PLCβ4, and PLCγ1 in brain function and brain disorders.

2. Epilepsy

Epilepsy is a chronic neurological disorder characterized by the repeated occurrence of seizures due to dysregulation of neuronal activity. Epilepsy can occur due to a number of reasons, however for most patients the cause is unknown and the exact molecular and cellular basis for the neuronal abnormality is not fully understood (Chang and Lowenstein, 2003). Notably, genetic studies have reported an association of PLCβ1 and PLCγ1 with epilepsy. In a study using PLCβ1−deficient mice, early-onset severe tonic seizures were observed (Kim et al., 1997). Electrical stimulation of adjacent granule cells in the hippocampus resulted in cell death of hilar interneurons containing somatostatin (Sloviter, 1987). In PLCβ1-deficient mice, loss of somatostatin-containing hilar interneurons resulted in hippocampal hyperexcitability. Muscarinic acetylcholine receptors, in particular M_1, M_3, and M_5, are G protein-coupled receptors (GPCRs) that couple to Gq/11. Gαq activates PLCβ1 and mediates multiple functions including cholinergic seizures, locomotion, and drug addiction (Nathanson, 2000). In agreement with previously published results, disruption of PLCβ1 impairs signaling mediated by muscarinic acetylcholine receptors (mAChRs) (Kim et al., 1997). Consistent with the epileptic phenotype of PLCβ1 homozygous knockout mice, infantile epileptic encephalopathy is associated with the first homozygous loss-of-function PLCβ1 gene mutation in humans (Kurian et al., 2010). A study by Annapurna et al., observed a homozygous deletion of the PLCβ1 gene in a patient with malignant migrating partial seizures during infancy (Poduri et al., 2012). Collectively, these findings suggest a role for PLCβ1-mediated signaling in the development of epileptic seizures.

Brain-derived neurotrophic factor (BDNF) mRNA and protein levels are significantly elevated in the hippocampus of individuals with epilepsy (Murray et al., 2000; Takahashi et al., 1999). In addition, BDNF-mediated tropomyosin receptor kinase B (TrkB) activation was reported in a limbic epilepsy animal model (Danzer et al., 2004). Neuron-specific TrkB-deficient mice and transgenic mice overexpressing BDNF demonstrated that TrkB activation is required for epileptogenesis (Croll et al., 1999; He et al., 2004). These results also suggest that BDNF-TrkB-mediated downstream signaling is critical for epileptogenesis. PLCγ1 is a key mediator for TrkB receptor signaling and activation of TrkB-PLCγ1 signaling is induced in a kindling model (Kaplan and Miller, 2000). $TrkB^{PLC/PLC}$ knock-in mice lacking TrkB-PLCγ1 docking sites and PLCγ1 heterozygous mice both had reduced limbic epileptogenesis [13, 25]. These results suggest that PLCγ1-mediated signaling is necessary for limbic epilepsy.

Absence seizures are a type of generalized nonconvulsive seizures, and are characterized by a brief loss and return of consciousness. Absence seizures occur mainly in children and typically for short periods of time (Snead, 1995). The thalamocortical neuronal circuit gives rise to the epileptic spike-wave discharges (SWD), which are the electroencephalographic hallmarks of absence epilepsy (Huguenard and McCormick, 2007). PLCβ4 is detected at high levels in the thalamus, which is integral to the neurophysiology of absence seizures. (Watanabe et al., 1998). Importantly, thalamocortical-specific PLCβ4 knockdown and PLCβ4 whole-body knockout mice had spontaneous absence seizures with simultaneous behavioral arrests and appearance of spontaneous spike-wave discharges (SWDs). Notably, T-type Ca^{2+} channels in the thalamocortical neurons were found to be involved in the SWDs in these mice (Cheong et al., 2009).

3. Schizophrenia

Schizophrenia is a brain disorder that interferes with cognitive functions such as attention, motivation, execution, and emotion. The complexity of the mechanisms underlying schizophrenia is related to several brain regions that are affected (e.g., prefrontal cortex, hippocampus, and amygdala) (Shenton et al., 2001). Although the molecular mechanisms underlying schizophrenia pathophysiology are still not fully understood, genetic and molecular studies have identified a number of susceptibility genes and related pathways including dopaminergic (Seeman and Lee, 1975), serotoninergic (Lopez-Figueroa et al., 2004), muscarinic (Dean et al., 1996), and glutamatergic signaling (Nudmamud-Thanoi and Reynolds, 2004). Remarkably, prolonged stimulation of dopamine or SKF83959 (a D1-D2 dopamine receptor agonist) induced neuronal apoptosis through PLC-mediated signaling in cortical neurons (Zhang et al., 2011). In addition, PLCβ1 is involved in muscarinic receptor signaling (Kim et al., 1997) in the hippocampus and in glutamate receptor (mGluR5)-mediated signaling in the neocortex (Hannan et al., 2001). Altered PLCβ1 expression was observed in the prefrontal and superior temporal cortex of patients with schizophrenia, suggesting the involvement of PLCβ1-mediated signaling in schizophrenia pathogenesis (Lin et al., 1999). Furthermore, a deteriorated serotonin2A receptor-(Gqα)-PLCβ1 cascade was found in the left, but not right, superior temporal gyrus of schizophrenia patients (Shirakawa et al., 2001). The critical role of PLCβ1 in schizophrenia pathogenesis is supported by the observation of PLCβ1 gene deletions (Lo Vasco et al., 2012) and decreased PLCβ1 mRNA levels in the dorsolateral prefrontal cortex in schizophrenia patients (Udawela et al., 2011). Consistent with these observations, PLCβ1 knockout mice showed abnormal behaviors associated with schizophrenia including hyperactivity, impaired prepulse inhibition of the acoustic startle response, abnormal social behaviors, as well as a lack of barbering and nesting behavior. (Koh et al., 2008; McOmish et al., 2008). Abnormal behaviors observed in PLCβ1 knockout mice were also associated

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with muscarinic acetylcholine, vasopressin V1b, oxytocin, and metabotropic glutamatergic receptor, which are linked to GPCR-PLCβ1 signaling (Koh, 2013).

Several studies suggest that BDNF-TrkB signaling is important for schizophrenia pathogenesis. Levels of BDNF and TrkB mRNA were reduced in the prefrontal cortex of schizophrenia patients, indicating altered BDNF-TrkB signaling in schizophrenia pathogenesis (Hashimoto et al., 2005; Weickert et al., 2003). In addition, PLCγ1-mediated signaling affects N-methyl-D-aspartate receptor (NMDAR) regulation through neuregulin 1 (NRG1) (Gu et al., 2005), a schizophrenia susceptibility gene (Stefansson et al., 2002; Yang et al., 2003). The relevance of TrkB-PLCγ1 and NRG1-ErbB4 (NRG1 receptor) signaling is important in schizophrenia pathogenesis (Pandya and Pillai, 2014). These findings have implicated a possible involvement of TrkB-PLCγ1 signaling in schizophrenia pathogenesis.

4. Bipolar disorder

Bipolar disorder (BD) is a neuropsychiatric disorder characterized by manic and depressive episodes. Clinical and genetic studies have identified susceptibility genes for BD (Baum et al., 2008; Sklar et al., 2008; Wellcome Trust Case Control, 2007). Radhakrishna et al. observed a BD susceptibility locus on chromosome 20p11.2-q11.2, which encodes alpha-2 adrenergic receptors, a G protein subunit, and two enzymes. One of these enzymes is PLCγ1, which is involved in the phosphatidylinositol cycle. Lithium, a drug for BD, was identified as a chemical that inhibits the phosphatidylinositol cycle, providing further evidence to support the theory that PLCγ1 is associated with BD (Radhakrishna et al., 2001). Consistent with this, BD patients who are excellent responders to lithium treatment have a dinucleotide repeat in the PLCγ1 genomic region (Turecki et al., 1998). Since the dinucleotide repeat is located within the intron region with no obvious functional relevance, this finding indicates that specific alleles of this repeat may be in linkage disequilibrium with a nearby polymorphism that influences BD pathogenesis. Further studies found three polymorphic sites localized in three different exons of the PLCγ1 gene (Ftouhi-Paquin et al., 2001). However, this finding was not confirmed in a sample population of lithium-treated bipolar Norwegian patients. This population showed a significant increase in PLCG1-8 repeats only among lithium responders compared with the control subjects, based on analysis of the presence or absence of different dinucleotide alleles (Lovlie et al., 2001). Several studies suggest that BDNF, an activator of PLCγ1 signaling, plays a role in the onset and treatment of BD. Serum BDNF levels are decreased in both the depressive and manic phases, indicating that PLCγ1 signaling is reduced during BD pathogenesis (Cunha et al., 2006; Sklar et al., 2002). Thus, BDNF has been identified as a potential risk allele for BD (Okada et al., 2006).

5. Huntington's disease

Huntington's disease (HD) is a late onset, hereditary neurodegenerative disorder that causes uncontrolled movements, emotional issues, and impaired cognition. Huntington's disease is caused by an expanded, unstable trinucleotide repeat in the huntingtin (*htt*) gene. This mutation is translated into a stretch of glutamine residues near the amino terminus of *htt*, which results in a toxic gain of function, particularly in the striatum and cortex (Gusella and MacDonald, 2000). Several complex molecular mechanisms mediate dysfunction and death of striatal neurons. Of these mechanisms, a number of studies have suggested that BDNF controls survival and function of striatal neurons and that BDNF-TrkB signaling plays a crucial role in HD pathogenesis (Baquet et al., 2004; Gorski et al., 2003). In support of these studies, BDNF expression levels were reduced in caudate neurons, but not in cortical neurons in subjects with HD (Ferrer et al., 2000). These results indicate that BDNF-TrkB-PLCγ1 signaling consequently affects HD pathogenesis. In support of these findings, R6/1; $BDNF^{+/-}$ mice (HD model mice (R6/1) with lower BDNF levels) showed earlier and accentuated cognitive impairment compared to R6/1 mice with hippocampal long term potentiation (LTP) impairment (Giralt et al., 2009). Previous studies also support the important role of PLCγ1 in hippocampal LTP (Minichiello et al., 2002).

Gene expression profiling (GEP) analysis of HD peripheral tissue skin fibroblasts found that mRNA levels of PLCβ4 are upregulated in HD fibroblasts compared with control cells. Although further studies will be necessary to demonstrate the role of PLCβ4 in HD, the current findings suggest the possible involvement of PLCβ4-mediated signaling in HD development (Marchina et al., 2014).

6. Depression

Depression (major depressive disorder) is a common and serious mood disorder. Reduced neuron volume and neuronal loss are induced under stress and depression conditions in the hippocampus. The altered hippocampus is normalized by chronic antidepressant treatment (Warner-Schmidt and Duman, 2006). Interestingly, antidepressant treatment elevates BDNF levels while simultaneously alleviating depression (Duman, 2002; Dwivedi et al., 2005), and induces activation of TrkB-PLCγ1 signaling (Rantamaki et al., 2007). Antidepressant treatment also enhances phosphorylation of CREB, which is downstream of the TrkB-PLCγ1 signaling pathway. CREB overexpression in the hippocampus results in antidepressant-like behavioral effects in rats (Chen et al., 2001). In support of these findings, the brains of suicide victims, most of who suffer from depression, exhibited reduced expression of BDNF compared with health brains (Karege et al., 2005).

A pathway-based analytical strategy, observed 17 significantly enriched pathways associated with depression. Of these, the PLCβ1-related signaling pathway was mainly associated with depression (Kao et al., 2012). Interestingly, microarray

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analysis showed that chronic treatment with quetiapine (QTP), which has antidepressant-like action, altered the PLCβ1 mRNA level, which, was the molecular target of QTP (Orsetti et al., 2009). These results support the association of PLCβ1 with depression.

7. Alzheimer's disease

Alzheimer's disease (AD) is an age-associated neurodegenerative disorder with progressive memory loss and cognitive decline. AD is microscopically characterized by extracellular amyloid plaques and intraneuronal neurofibrillary tangles consisting of amyloid-β (Aβ) peptides and tau (microtubule-associated protein), respectively. In the tau hypothesis, tau tangles first destroy nerve cells and disrupt their normal function, which is critical for memory (Aleong et al., 2003; Querfurth and LaFerla, 2010). Notably, tau binds to the SH3 domain of PLCγ1, suggesting the physiological relevance of PLCγ1 in AD pathogenesis (Jenkins and Johnson, 1998; Reynolds et al., 2008). In addition, tau proteins together with arachidonic acid activate PLCγ1 activity *in vitro*. These results suggest that activation of cytosolic PLA2, a mediator of agonist-induced arachidonic acid release, might be required for tau-induced PLCγ1 activity in neuronal cells. (Hwang et al., 1996). Consistent with these observations, PLCγ1 was reduced significantly in the membraneous fraction of AD cortical tissues (Shimohama et al., 1995).

A number of studies have suggested the involvement of BDNF-TrkB signaling in AD. BDNF mRNA and protein levels as well as BDNF-TrkB signaling were reduced in the hippocampus and neocortex in a brain affected by AD (Allen et al., 1999; Connor et al., 1997; Fahnestock et al., 2002; Ferrer et al., 1999). BDNF protects against oligomeric amyloid-β 1–42 peptide-induced cell death in neuronal cells (Kitiyanant et al., 2012). Furthermore, tau dephosphorylation is induced by BDNF (Elliott et al., 2005). Although direct evidence for the role of PLCγ1 in AD pathogenesis is still lacking, previous studies related to BDNF-TrkB signaling in AD strongly suggest the involvement of PLCγ1 in AD pathogenesis.

8. Conclusion

The activation of primary PLCs regulates various signaling events in the brain. Among primary PLCs, PLCβ1, PLCβ4, and PLCγ1 are highly detected in the brain. Different distribution and regulation mechanism of each primary PLC isozyme contribute to their specific role in different regions of the brain. Although the results of many studies suggest the association of primary PLCs with various brain disorders, many questions still remain. We now need to understand more precisely the mechanism underlying how each primary PLC is involved in pathogenesis of brain disorders for the treatment of psychiatric and neurodegenerative disorders.

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