Biochimica et Biophysica Acta xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbalip

Review

PIPs in neurological diseases ☆

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ARTICLE INFO

Article history:
Received 14 November 2014
Received in revised form 29 January 2015
Accepted 1 February 2015
Available online xxxx

Keywords:
Phosphatidylinositol
Lipid
Disease
Brain
Endosome
Membrane

ABSTRACT

Phosphoinositide (PIP) lipids regulate many aspects of cell function in the nervous system including receptor signalling, secretion, endocytosis, migration and survival. Levels of PIPs such as PI4P, PI(4,5)P_2 and PI(3,4,5)P_3 are normally tightly regulated by phosphoinositide kinases and phosphatases. Deregulation of these biochemical pathways leads to lipid imbalances, usually on intracellular endosomal membranes, and these changes have been linked to a number of major neurological diseases including Alzheimer's, Parkinson's, epilepsy, stroke, cancer and a range of rarer inherited disorders including brain overgrowth syndromes, Charcot–Marie–Tooth neuropathies and neurodevelopmental conditions such as Lowe's syndrome. This article analyses recent progress in this area and explains how PIP lipids are involved, to varying degrees, in almost every class of neurological disease. This article is part of a Special Issue entitled Brain Lipids.

1. Introduction

Phosphoinositides (PIPs) are structurally related and functionally diverse phospholipid molecules with many important roles in the nervous system. These functions include substrate supply to receptor-stimulated phospholipase C (PLC) and phosphoinositide 3-kinase (PI3K) signalling pathways, ion channel regulation, the control of intracellular vesicular trafficking, cytoskeletal organisation and protein-mediated inter-organelle lipid transport [1,2]. Excluding the parent molecule phosphatidylinositol (PI) there are seven different lipids in the PIP family, consisting of PI4P, PI(4,5)P_2, PI(3,4,5)P_3, PI(3,4)P_2, PI(3,5)P_2, PI3P and PI5P. The different PIPs are formed by a collection of phosphoinositide kinase and phosphatases that catalyse the stepwise phosphorylation and dephosphorylation of hydroxyl groups on different positions of the inositol head group (Fig. 1) [3]. In the nervous system, as in other mammalian tissues, the highest mass levels are for PI, followed by PI4P and PI(4,5)P_2, with much lower and often transient agonist-stimulated peaks of the D3-phosphorylated lipids formed through receptor-activated phosphoinositide 3-kinase pathways [3].

1.1. Signalling by PI4P and PI(4,5)P_2

Levels of PI4P and PI(4,5)P_2 undergo rapid depletion and resynthesis following agonist activation of heterotrimeric G protein-coupled receptors (GPCRs) that signal through PLCβ. PLC activation, usually initiated via Gα_q subunits, induces substantial PI(4,5)P_2 hydrolysis and results in the formation of the second messengers inositol(1,4,5)-trisphosphate and diacylglycerol that mediate Ca^{2+} release from the endoplasmic reticulum and also PKC activation. GPCRs that signal through this route are high-profile drug targets in the treatment of neurological diseases. Examples include Alzheimer's disease where both orthosteric and allosteric ligands for the M1 muscarinic receptor [4] have been developed for the treatment of cognitive defects [5] and to inhibit the formation of neurofibrillary tangles and β-amyloid plaques [4,6,7]. Similarly, PLC-coupled delta opioid receptors are pharmacological candidates for chronic pain, epileptic seizures and locomotor disorders [8,9]. Whilst GPCR-specific ligands and individual receptor expression patterns in the CNS facilitate the targeting of specific cell types and processes, drugs that inhibit PIP-metabolising enzymes also have some potential in the treatment of neurological diseases. Examples include the recent development of isoform-specific small molecule inhibitors of the PI(4,5)P_2-metabolising enzymes PLCβ3 [10] and PIP5K1C [11] for the treatment of chronic pain.

1.2. PI 4-kinases in the CNS

Cellular PI4P levels are maintained by a family of four different PI 4-kinase (PI4K) enzymes: PI4K2A, PI4K2B, PI4KA and PI4KB (Fig. 2). All four PI4K isozymes are expressed in the nervous system but they are targeted to different subcellular compartments including the

Abbreviations: Aβ, amyloid β protein; CMT, Charcot–Marie–Tooth; GPCR, G protein-coupled receptor; PICALM, phosphatidylinositol binding clathrin assembly protein; PIPs, phosphoinositides, PI3K, phosphoinositide 3-kinase; PI4K, phosphatidylinositol 4-kinase; PLC, phospholipase C; PH domain, pleckstrin homology domain, PIPK, PI4P 5-kinase

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http://dx.doi.org/10.1016/j.bbalip.2015.02.002
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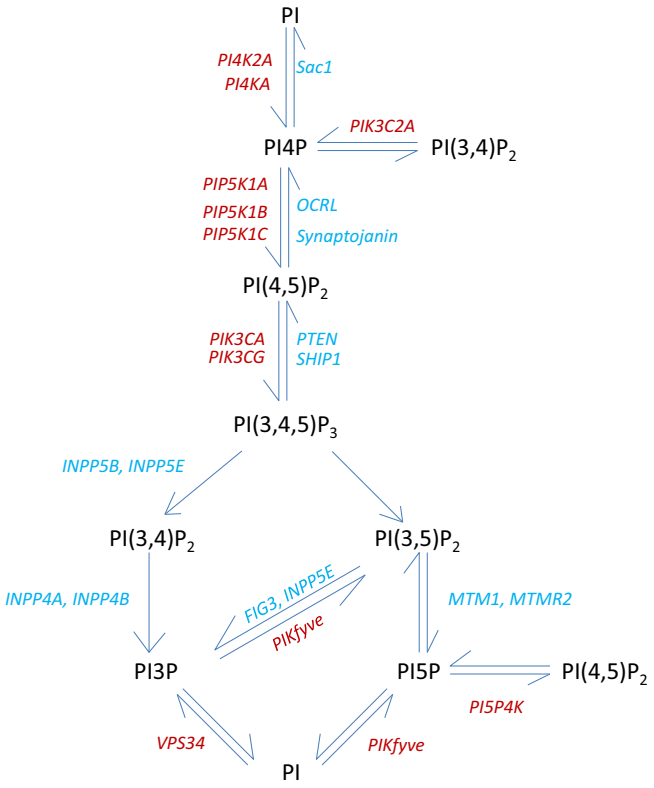

Fig. 1. Diagram illustrating PIP metabolic pathways in the CNS and the enzymes that have been implicated in neurological diseases. Note that lipid kinases appear in red and phosphatases in blue.

trans-Golgi network (TGN), endosomes, secretory vesicles and the plasma membrane [12,13]. More recent work investigating the pathways that supply PI4P to plasma membrane signalling processes has revealed that multiple PI4K isoforms at different cellular locations are required to maintain the signalling pools of PI4P and PI(4,5)P_2 [14,15]. PI4K2A, the crystal structure of which has been solved [16,17], is by far the most abundant PI kinase activity measurable in brain membranes [18] and has been implicated in TGN-endosomal sorting [19–24] and cell survival [18]. However, non-neuronal studies indicate that the wortmannin-sensitive PI4KA is likely to be the dominant isozyme for synthesising the PI4P required for agonist-dependent signalling [25,26].

When considering the role of any PIP pathway in neurological disease it is important to note that each phosphoinositide-metabolising enzyme appears to possess a distinct protein interactome that operates in combination with catalytic activity to define its overall function in neuronal signalling and trafficking [13]. A well-studied example to illustrate these layers of complexity is PI4K2A, which synthesises a pool of PI4P on TGN and endosomal membranes, and which has also been visualised on secretory vesicles [22,23,27–32]. This enzyme contains an amino acid motif that can bind the E3 ubiquitin ligase itch and this interaction facilitates reciprocal regulation of both enzymes' catalytic activities [33]. This intermolecular association thereby functionally associates rates of endosomal ubiquitination with membrane PI4P synthesis, and PI4P-dependent signalling and trafficking with protein targeting for degradation.

In addition to effects on protein ubiquitination, the modular protein-binding functions of PI4K2A influence membrane sorting in TGN endosomal trafficking. PI4K2A contains a dileucine AP-3 clathrin adaptor-binding motif that partly mediates non-catalytic PI4K2A functions in cargo sorting and trafficking from the TGN to late endosomes [19]. Furthermore, PI4K2A has been shown in cross-linking and proteomic studies to be a component of the multi-protein, biogenesis of lysosome-related organelles complex-1 (BLOC-1) and also the Wiskott Aldrich Syndrome protein and scar homologue (WASH) complex that regulates the actin cytoskeleton [34]. In addition, PI4K2A has been shown to be a protein-binding partner for the R-SNARE protein VAMP3 [24]. Therefore, it is likely that alterations to PI4K2A expression can have ramifications for the numerous components of its associated protein interaction network and that these, in turn, can impact on the multiple neuronal roles that have been ascribed to this protein [20,34–38]. There is also evidence for PI4K2A activation by the transcription factor c-FOS, which represents a novel avenue for research and potentially links alterations to PI4P synthesis with genomic transcriptional regulation [39,40].

In conjunction with a repertoire of protein binding partners, post-translational modifications of PI4K2A are important for its intracellular trafficking functions. Recently, PI4K2A has been shown to be phosphorylated by GSK3 and this regulates PI4K2A-dependent trafficking of AMPA receptors by promoting the binding of the AP-3 clathrin adaptor [41]. The catalytic activity of PI4K2A is also regulated by post-translational modification. The rate of PI4P synthesis by PI4K2A is determined by non-covalent membrane interactions and the palmitoylation of two cysteine residues within the catalytic domain of the protein [42–45]. The membrane lipid environment and particularly the cholesterol content of these membranes can affect the enzyme's catalytic activity [27,46–48] and palmitoylation state, since the late Golgi-localised palmitoyl transferases that modify PI4K2A are also cholesterol sensitive [45]. Targeting of PI4K2A to cholesterol-rich membranes is also important for its proposed role in regulating OSBP-dependent sphingomyelin synthesis at this subcellular location [49]. Hence, PI4K2A is an example of a single PI-utilising enzyme that integrates a membrane environment-sensitive catalytic function with a diverse range of non-catalytic functions that include protein targeting for degradation, endosomal trafficking and non-vesicular lipid transport, all of which are relevant to PIP disease pathways in the CNS.

1.3. Generation of PI(4,5)P_2 in the brain

Resynthesis of PI(4,5)P_2 requires PI4P 5-kinase activity by three main isozymes, PIPK1A, PIPK1B and PIPK1C (Fig. 2). Whilst evidence demonstrates that PIPK1A negatively regulates neurite outgrowth [50] and PIPK1B growth cone morphology [51], in the CNS at least, isoform-specific knockout studies in mice have revealed a dominant role for PIPK1C isozymes in PI(4,5)P_2 generation [11,52,53]. PI(4,5)P_2 can also be generated through the D4 phosphorylation of PI5P by PI5P 4-kinases [54]. PI5P can be synthesised by D5 phosphorylation of PI by PIKfyve (also known as Fab1) [55–57], but there is strong recent evidence that in cells PIKfyve phosphorylates PI3P to PI(3,5)P_2, which is then dephosphorylated via 3-phosphatase activity to generate PI5P [58]. PI5P is a much less abundant lipid substrate than PI4P and hence, PI5P is not the major source of cellular PI(4,5)P_2 in the brain.

1.4. PIP 5-kinase mutations in neurological diseases

To date, there is only one direct example of a genetic mutation in either a PI4K or PIP 5-kinase causing a human disease and that is PIP5K1C in the rare autosomal recessive disorder lethal muscle contractural syndrome type 3 [59]. However, there has been an interesting development recently concerning the possible involvement of PIP5K1B in Friedreich's ataxia [60], a multisystem disease that features pronounced neurodegeneration. The PIPK1B gene had previously been implicated as the cause of this disorder but subsequent papers revealed that this was probably a misidentification and concluded instead that Friedreich's ataxia was due to silencing of the FTX gene which encodes the mitochondrial protein frataxin [61,62]. However, Bayot and colleagues [60] have reported that the GGA triplet repeat expansion that silences frataxin gene also results in cis-silencing of PIPK1B, leading to diminished PI(4,5)P_2 production and striking disorganisation of the

Please cite this article as: M.G. Waugh, PIPs in neurological diseases, Biochim. Biophys. Acta (2015), http://dx.doi.org/10.1016/j.bbalip.2015.02.002