PIPs in Neurological Diseases

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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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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.

Keywords: Phosphatidylinositol; lipid; disease; brain; endosome; membrane.

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1.0 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 (Figure 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 $G\alpha_q$ 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]. While 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 (Figure 2). All four PI4K isozymes are expressed in the nervous system but they are targeted to different subcellular compartments including the *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 synthesizing 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 (Figure 2). While 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 a 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 actin cytoskeleton [60]. These observations indicate that genetic impairment of PIPK1B function could contribute to some of the complicated clinical presentations of this ataxia.

2.0 The channelopathies and disorders of PIP binding

In addition to their roles in substrate supply to the PLC and PI3K signalling pathways [63], D4-phosphorylated PIPs have important roles in ion channel regulation at the plasma membrane [15, 64-79]. Lipids such as PI(4,5)P_2 and PI4P can either positively or negatively [80] influence ion flux. This occurs through interactions with specific sites on channel proteins or through effects on membrane charge, and frequently in tandem with other modulators such as heterotrimeric G proteins subunits or subunit phosphorylation [73, 74, 81-83]. This lipid-based regulatory mode is relevant to neurological diseases since important pharmacological targets, for example, the KCNQ channel in epilepsy, are regulated by membrane PIP levels [76]. Furthermore, dysfunctional channel-PIP interactions, usually due to genetic mutations affecting channel protein structure, lead to deregulated neuronal transmission. Diseases that feature this type of molecular mechanism are often collectively referred to as channelopathies.

One well-established example of a channelopathy involving PIPs is a potassium-sensitive periodic paralysis with associated ventricular arrhythmias known as Andersen-Tawil syndrome [84-87]. This can be either an autosomal recessive disorder or occur sporadically and is caused by point mutations in PIP interaction sites on the KCNJ2 (Kir2.1) inwardly-rectifying potassium channel. Interestingly, while PI(4,5)P_2 activates KCNJ2 opening the binding of other membrane PIP species inhibit this process by directly competing out PI(4,5)P_2 binding [88]. Structural analysis of the protein family has revealed the presence of two distinct PIP interaction sites on the channel protein. The first PIP interaction site consists of a conserved non-specific phospholipid-binding region in the

transmembrane domain and a second site, located in the channel's cytoplasmic tail, specifically binds $PI(4,5)P_2$ [89]. Conversely, for potassium channels such the TRPV4 that are negatively regulated by $PI(4,5)P_2$ binding, in this case via lipid biding to an ankyrin homology domain, mutations of the PIP interaction site result in augmented channel function [80], and this is relevant to TRPV4 channelopathies such as Charcot-Marie-Tooth (CMT) type 2C and congenital distal and scapuloperoneal spinal muscular atrophy [80, 90-93].

Another corollary of these recent insights is that the intramembrane balance of PI4P and $PI(4,5)P_2$ is likely to be an important determinant of ion channel gating. Furthermore, distortions of this ratio, as can occur in inherited conditions characterised by $PI(4,5)P_2$ phosphatase dysfunction, may be sufficient to cause ion channel deregulation [94, 95]. However, this is hitherto an underexplored area of neurological research. It is also important to mention that PIPs can influence ionotropic neurotransmission through vesicular trafficking processes that deliver, recycle and degrade plasma membrane-localised receptors, channels [13] and neurotransmitter transporter proteins [96]. These PIP-dependent processes have repercussions for receptor reserve and thus agonist efficacy, and collectively represent another route through which PIPs can modulate synaptic signalling.

While much attention has focused on K^+ channel regulation by PIPs, there is also a role for D3-phosphorylated PIPs in this aspect of neurophysiology [97]. The best studied disease in this regard is mucolipidosis type IV, an autosomal recessive neurodegenerative disorder that can be caused by mutations in the $PI(3,5)P_2$ interaction site on the TRPML1 channel, which localises to intracellular late endosomal/lysosomal membranes where it mediates metal cation efflux [98-100]. Significantly, a recent publication has described the development of small molecule activators of TRPML1 that can restore the function of $PI(3,5)P_2$-insensitive structural variants that are also associated with the mucolipidosis phenotype [101]. This report sets an important precedent and indicates that molecules targeting PIP-channel interactions may be an important area for future drug development in neurodegenerative diseases.

2.1 Role of PIP protein binding domains in neurological diseases

A recent proteomics study identified 405 PIP-interacting proteins, which unexpectedly means that this set of proteins is more numerous than the entire complement of proteins involved in either phosphoprotein or ubiquitin binding [102]. PIPs can influence a wide range of processes in neurons through the membrane recruitment of proteins containing either PI4P- or PI(4,5)P_2-binding domains such as the PIP-specific pleckstrin homology (PH) domains, epsin N-terminal homology (ENTH) and AP180 N-terminal homology (ANTH) domains, and PX and FYVE domains [103]. These specific inter-molecular interactions facilitate the spatial and temporal targeting of signalling proteins such as PLCγ and Akt during agonist-stimulated PIP signalling, and also the recruitment of membrane trafficking machinery such as epsin-1, AP-2, AP180 and dynamin to the plasma membrane for clathrin-mediated coated pit formation and endocytosis.

PI4P has an important role in targeting, via PH domain binding, lipid transfer proteins such as OSBP, CERT and FAAP2 to PI4P-enriched membranes at points of inter-organelle contact sites (reviewed in [13]). Furthermore, the recent finding that PI4P hydrolysis by Sac1 phosphatase releases energy to facilitate non-vesicular cholesterol transfer at Golgi-endoplasmic reticulum contact sites suggests an additional role for PIPs as a membrane-associated source of energy [104]. The implications of this unexpected finding for neurological diseases have yet to be explored but it is relevant to note that intracellular levels of lipids transported by PI4P-dependent processes, such as glucosylceramide, are frequently abnormal in diseases such as Parkinson's and Gaucher's [105].

There are some instances in the literature of mutations in protein PH domains causing neurological and neuromuscular diseases. The best-studied example is the PI(4,5)P_2-binding PH domain of dynamin 2, a GTPase required for the scission of clathrin-coated pits to form clathrin-coated vesicles during endocytosis and also the release of clathrin-coated transport vesicles during Golgi-to-endosomal intracellular trafficking. A point mutation (K562E) in the dynamin 2 PH domain that

abolishes PI(4,5)P_2 binding is associated with a dominant intermediate form of CMT neuropathy [106]. CMT disease describes a spectrum of progressive peripheral neuropathies with varying degrees of severity that can be caused by mutations in at least 60 genes affecting a number of biochemical pathways [107]. Mutations within the PH domain of this dynamin isoform have also been found in patients affected by other variations of CMT disease and also centronuclear myopathy [108-116]. However, it is important to note that not all disease-causing mutations within the dynamin PH domain also cause impaired PI(4,5)P_2 binding [114]. Moreover, this type of disease association is not exclusive to dynamin isoforms and there are now several reports demonstrating that mutations in the PH domains of PLEKHG5 can also give rise to CMT symptoms [117, 118] and paediatric-onset lower motor neuron disease [119].

3.0 CNS disorders caused by PI4P and PI(4,5)P_2 imbalances

There are examples of inherited but rare multisystem diseases caused by loss of function mutations in the PIP 5-phophatases and these have been extensively discussed in recent reviews of this area [120-123]. Of particular note in a neurological context is oculocerebrorenal syndrome of Lowe, sometimes referred to as Lowe's syndrome or OCRL [124]. This is an X-linked recessive disorder and therefore only affects males. In addition to deleterious effects on the eyes and kidneys, OCRL presents clinically with neurological problems including intellectual impairment, developmental delays and behavioural problems. This disease is caused by loss of function mutations in the OCRL gene, which encodes a multidomain PIP 5-phosphatase that dephosporylates PI(4,5)P_2 to produce PI4P [125-131]. OCRL has been localised to endosomes, the Golgi apparatus, the plasma membrane, phagosomes [132] and, importantly in terms of understanding current thinking on the disease mechanism, clathrin-coated vesicles [133]. Loss of OCRL activity leads to the build-up of PI(4,5)P_2 on endosomal membranes and this feature of the disease drives actin accumulation and cytoskeletal abnormalities [134-138]. It is worth noting though that the case for PI(4,5)P_2 accumulation underlying the neuropathological defects in OCRL is not proven. This is because Dent's disease,

which is also caused by OCRL dysfunction, does not feature CNS involvement [136, 139, 140]. From this point of view, it is useful to consider how the non-catalytic functions of the OCRL protein might contribute toward the disease symptoms. Of particular interest in this regard is the PH domain of OCRL which does not bind PIPs but which instead contains a clathrin-interacting motif, and it is this motif that targets OCRL to late-stage clathrin-coated pits during endocytosis [137, 141]. OCRL1a, a splice variant only expressed in the brain, has a higher affinity for clathrin than the more ubiquitously expressed OCRL1b variant, and thus it may be specifically the loss of this protein-interaction function that causes the neurological defects associated specifically with OCRL as opposed to Dent's disease [142]. Reports that non-catalytic mutations in the APPL1-binding domain of OCRL are pathological [143] further support the idea that the phenotype of Lowe's disease may be an aggregate manifestation of deficiencies in the OCRL1 protein interactome in tandem with abrogated $PI(4,5)P_2$ homeostasis [144].

When considering the role of OCRL in degrading $PI(4,5)P_2$, it is important to remember that there are other neuronal PIP phosphatases such as PIPP (INPP5J) and SHIP2, which can catalyse the D5 dephosphorylation of both $PI(4,5)P_2$ and $PI(3,4,5)P_3$ but have nevertheless not yet been implicated in any OCRL-like pathology [120]. Furthermore, mutations of the PIP D5 phosphatases synaptojanin proteins (SYNJ1 and SYNJ2), which have roles in decoating clathrin-coated vesicles, do not feature in either Lowe's or Dent's disease. Hence although speculative, and notwithstanding some differences in PIP substrate preferences, these observations suggest very specific and non-overlapping roles for the D5 phosphatases in neuronal physiology and that dysfunction of these enzymatic pathways in neuronal disease cannot be explained simply by abrogated $PI(4,5)P_2$ degradation. Instead, alterations to the non-catalytic functions of these enzymes, and also perhaps the highly localised changes to the minor endosomal pools of $PI(4,5)P_2$ in the membrane domains where these proteins are specifically and temporally targeted, may hold the key to understanding how loss of function in PIP degradation leads to particular patterns of neurodegenerative disease.

4.0 Defective PI 3-kinase signalling in neurological disease – overgrowth and myelination disorders

Phosphorylation of PI(4,5)P_2 on the D3 position by class I PI3K catalytic subunits (PIK3CA, PIK3CB, PIK3CD and PIK3CG) can generate PI(3,4,5)P_3, a molecule with important roles in both pro-survival [145-147] cell migration signaling [148]. Phosphorylation of either PI4P or PI by class II PI3Ks such as PIK3C2A produces respectively PI(3,4)P_2, a PIP species recently implicated in clathrin-mediated endocytosis [149] and also PI3P, which functions in primary ciliogenesis [150]. Individual PI3K isoforms can have multiple roles in the CNS. As an example of this diversity in neuronal functions, PIK3CG (more commonly referred to as PI3Kγ) is required to maintain blood-brain barrier integrity during ischaemic reperfusion [151], has a function in memory and behaviour through NMDA receptor-stimulated long-term potentiation [152] and is a drug target in neuroinflammatory diseases such as multiple sclerosis [153].

In the nervous system, PI3K activity can be stimulated either by receptor tyrosine kinases or GPCRS; examples include insulin receptors activating PIK3CA isoforms or metabotropic glutamate receptors signaling via PI3KCB (reviewed in [154]). These signalling events dynamically control diverse physiological functions in the nervous system including protein synthesis [155, 156], long-term depression [152, 157, 158] and neuronal morphogenesis [159]. In healthy cells, the duration of PI(3,4,5)P_3 signalling is limited due to its rapid dephosphorylation by PIP phosphatases such as PTEN and SHIP2. Moreover, several neurological diseases arise from gain of function and amplified PI3K/Akt/mTOR signalling and this is principally due to deregulated and constitutive activation of PI3K isoforms or loss of PI(3,4,5)P_3 phosphatase activity.

These numerous PI3K functions in the CNS depend on the activation and membrane recruitment of protein kinases such as PDK1 and Akt isoforms and a range of effector proteins with PI(3,4,5)P_3- and PI(3,4)P_2-binding domains such as ARNO [160], which has been implicated in functions such as dendritic development. Significantly, a number of recent publications have revealed a crucial role for

$PI(3,4,5)P_3$-dependent processes [161] and the PI3K/Akt/PTEN/mTOR signalling axis in myelination [153, 162-175], which is a key process in maintaining neuronal transmission, survival and recovery from trauma.

4.1 PI3K and Akt3 link brain overgrowth with epilepsy and autism.

In terms of neurological disease, one of the most striking developments in this field has been the number of recent reports implicating activating mutations in enzymes such as PIK3CA and Akt3 in a variety of brain overgrowth syndromes such as megalencephaly. These disorders feature increased numbers of both neurons and glial cells [176-182] and recent discoveries in this area are challenging for ideas that PIK3CA activating mutations and/or PTEN deletion are sufficient to drive malignancy to such an extent that certain cancers could be considered 'addicted' to PI3K signalling [183].

Hemimegalencephaly is a rare disorder featuring overgrowth of only one cerebral hemisphere and severe epilepsy. This type of cortical dysplasia is characterised histologically by dysfunctional cellular proliferation, differentiation and mislocalisation of particular neuronal cell types including GABAergic neurons, which are often dysfunctional in epilepsy [184]. Recently, Lee and colleagues [176] discovered that surgically resected diseased tissue from patients suffering from this disease was subject to a number of somatic mutations expected to cause constitutive activation of PI3K signalling to mTOR. As these mutations were only found in diseased brain regions, the authors concluded that this syndrome could be classified as a genetic mosaic disease. The somatic activating mutations identified were in the PIK3CA, AKT3 and MTOR genes. Interestingly, unlike in cancer where the PIK3CA activating mutation H1047R predominates, in hemimegalencephaly the activating E545K mutation is more common. Other mutations include a substitution in the N-terminal PH domain of AKT3, which is known to result in increased activation of the enzyme [185]. The biochemical consequences of the mTOR C1483Y mutation are not yet known, but the authors found

that in least some of these cases there was activation of S6 phosphorylation indicating upregulation of Akt-mTOR signalling. Simultaneous with the report of PI3K/AKT involvement in hemimegalencephaly, Rivière and co-workers [180] reported a range of mutations in AKT3, the regulatory PI3K subunit PIK3R2, and again in the PIK3CA protein in a number of related megalencephalies . Several subsequent studies in this area have also found AKT3 gain of function mutations either by gene amplification [182] or the E17K activating point mutation [179], which taken together demonstrate a remarkable and common dependency for activated and brain-specific Akt3 signalling in a whole spectrum of cerebral overgrowth disorders. In terms of understanding how AKT3 drives these proliferative pathologies, there is strong evidence that that it is due to inhibited cyclin D2 turnover leading to cell cycle defects [186]. Of importance in this regard are the converse findings that *akt3* homozygous knockout mice have reduced brain size [187, 188] and that microcephaly in human disease is associated with haploinsufficiency of the chromosome 1q-localised *AKT3* gene [189].

An alternative means to amplify PI(3,4,5)P_3 signalling and pathological brain growth would be via a loss of function mutation in PTEN, and there are reports of both frameshift and point mutations in PTEN causing extreme megacephaly and severe epilepsy often associated with autism [190]. Other defects in this lipid pathway, caused by mutations in the D4 phosphatase INPP4A, which dephosphorylates PI(3,4)P_2 to PI3P, have been shown to cause NMDA receptor-mediated excitotoxic cell death, epilepsy and microcephaly [191-194]. In addition to revealing a major role for the PI3K signalling pathway in regulating brain development and size, there is now accumulating evidence that defective PTEN functioning and consequently mTOR activation are important in epilepsy and autism [190, 195-204]. Thus, enzymes in this pathway are candidate drug targets for non-surgical treatment of these neurological disorders.

4.2 Neurological involvement in PTEN germline mutations and benign tumour growth

Germline loss of function mutations in PTEN give rise to an array of clinical syndromes, all of which feature benign and disorganised tissue overgrowth manifesting as neoplasia (hamartoma). The tissues affected and the severity of the condition can be highly variable even between siblings [205], but when caused by a germline PTEN loss of function mutation this group of diseases, which include Bannayan-Riley-Ruvalcaba syndrome and Cowden syndrome, are collectively referred to as PTEN hamartoma tumour syndromes (PHTS) [206]. As with sporadic or somatic mutations in PTEN, macrocephaly together with a cognitive impairment and developmental delays are common findings in PHTS. More recent work has found that similar to some somatic cerebral overgrowth disorders, there are instances of PIK3CA and AKT mutations in some Cowden syndrome patients, indicating a potential for upregulated $PI(3,4,5)P_3$-dependent oncogenic transformation within affected tissues [207]. In line with this, there is a much increased risk of developing breast, thyroid, kidney, endometrial and colon cancers with PHTS [206, 208]. Neurological tumours such as neuromas [209] have sometimes been found in PHTS patients but it is not yet known how this relates mechanistically to PTEN gene anomalies.

4.3 Activated PI3K signalling: overgrowth versus glioma

The set of recent findings suggesting that PI3K pathway activations can cause brain overgrowth disorders but not necessarily cancer suggests the need for a critical re-evaluation of the proposed link between PTEN and glioma. The evidence for PTEN involvement in malignant brain tumours has accumulated over many years and for many cancers, there is a wealth of evidence from multiple studies indicating that PTEN is a tumour suppressor [210-216]. Furthermore, the genetic evidence for PTEN involvement in glioma is striking, with over 60% of advanced gliomas [215, 217-220] exhibiting genetic rearrangements leading to loss of PTEN function and knockdown studies on cultured cells demonstrating that ablated PTEN expression causes increased astrocyte proliferation and hypertrophy [221-223]. Many of the physiological roles attributed to PTEN concern the processes that arrange and organise the developing nervous system which, in turn, may relate to the

function of the enzyme in cell motility and adhesion [224-229]. A detailed characterisation of neuronal function in mice in which PTEN expression was ablated in neurons post-natally revealed that the main deficits were in synaptic plasticity and transmission, particularly in long-term potentiation and long-term depression, which manifested phenotypically as memory impairment [230]. Hence, in addition to developmental roles in organising the developing CNS, PTEN has physiological roles in neuronal transmission, indicating that changes to the enzyme's activity or expression can have multiple consequences that extend beyond cell proliferation.

Another point to consider is that unlike in PTEN overgrowth syndromes where there is often a single gene defect in PTEN or AKT, cancers are driven and evolve through several mutations, and for gliomas there is often co-upregulation of EGFR expression, leading to sustained receptor-driven signalling of not only PI3K but also other pro-oncogenic signalling pathways [210, 213, 231-244]. A switch to PTEN-dependent signalling is often a feature of more advanced tumours, possibly due to chromosome 10 loss of heterozygosity or resistance selection due to drug-induced inhibition of other proliferative pathways [214, 233, 234, 245]. In this way, upregulation of non-PIP oncogenic signalling networks may work in concert with PTEN deletions to generate a malignant phenotype and this may explain the mixed success so far in clinical trials of molecules that target solely upstream components of the receptor-PI3K signalling axis [246-251]. While PTEN is very well studied in glioma, other enzymes that can amplify PI3K signalling such as constitutively activating PIK3CA mutations [147, 212, 252, 253] also feature in many patients with this disease and indeed other neurological cancers including anaplastic oligodendrogliomas, anaplastic astrocytomas and medulloblastomas [254, 255].

5.0 PI(3,5)P_2 and Charcot-Marie-Tooth neuropathies

PI(3,5)P_2 is a quantitatively rare PIP that is found on endosomal membranes where it functions in the control of membrane fusion and dynamics [256]. PI(3,5)P_2 is formed via D5 phosphorylation of PI3P

catalysed by PIKfyve [58] and is then rapidly dephosphorylated back to PI3P by Sac3, a PI(3,5)P_2 5-phosphatase encoded by the FIG4 gene [55, 57, 257-264]. Alternatively, PI(3,5)P_2 can potentially be dephosphorylated to PI5P by as many as six of the catalytically active members of the myotubularin-related 3-phosphatase family i.e. MTM1 (mutated in X-linked recessive centronuclear myopathy) [265], MTMR2, MTMR3, MTMR4, MTMR6, MTMR7 and MTMR8 (reviewed in [266, 267]). Alterations to PI(3,5)P_2 levels in mice via knockout of the PIKfyve activator ArPIKfyve/Vac14 or Sac3/FIG4 phosphatase lead to substantial neurodegeneration, hypomyelination defects and abrogated intracellular trafficking [268-270]. There are now several examples of neurological diseases in humans, including most prominently particular presentations of CMT disease, which are caused by genetic mutations that affect PI(3,5)P_2 homeostasis [271].

In terms of alterations to PIP metabolism, loss of function mutations in enzymes that dephosphorylate PI(3,5)P_2 are prominent in the CMT4 subgroup of the disease, which is characterised by the paediatric onset of progressive axonal degeneration and associated myelin defects. Amongst the PI(3,5)P_2 phosphatases associated with CMT4 are MTMR2 (CMT4B2) and its structurally related but catalytically inactive protein binding partner MTMR13 [172, 267, 272-278]. Mutations in the PI(3,5)P_2 5-phosphatase Sac3/FIG4 that generates PI3P have also been implicated in CMT disease (CMT4J) [279], as well as other inherited neuropathies such as Yunis-Varón syndrome and amyotrophic lateral sclerosis [280, 281], all of which strengthen the case for a crucial physiological role for PI(3,5)P_2 in maintaining normal neuromuscular functions and in particular myelination. Since the low abundance PIPs PI(3,5)P_2, PI5P and PI3P are found mainly on endosomal and lysosomal membranes, these diseases are manifestations of defective PIP trafficking functions on these intracellular organelles that constitute the intracellular degradative trafficking pathway [256, 269]. This has led to the suggestion that these pathological examples of intracellular PI(3,5)P_2 dyshomeostasis could be considered as a class of endosomal-lysosomal storage disorder [282].

5.1 Cilliopathies (Joubert's and MORM syndromes) and INPP5E

INPP5E is a PIP 5-phosphatase that is highly active against $PI(4,5)P_2$, $PI(3,5)P_2$ and $PI(3,4,5)P_3$ [122, 283]. INPP5E localises to primary cilia [284, 285], which are single, microtubule-dependent, long, thin, membranous projections that are immotile and emanate from the centriole [286]. Primary cilia have been noted on many cell types including neurons [286-289] and while their functions are still being elucidated, they have been shown to function as specialised Ca^{2+} signalling organelles [290, 291] and are also an important site for Hedgehog signalling [292, 293]. Primary cilia from radial glia are important for the formation of the cerebral cortex during brain development [294] and processes such as dendritic arborisation [295] and neuronal migration [296]. Ciliary defects feature in a variety of neurodevelopmental disorders [297] and mutations in INPP5E have been implicated in Joubert's and MORM ciliopathies.

Joubert's syndrome is a ciliopathy characterised by abnormal development of the cerebellum and brainstem, which are identifiable as a signature 'molar tooth' structure when imaged [298]. Joubert's ciliopathy has been associated with mutations in at least nine different genes, amongst which are mutations in the PIP phosphatase domain of INPP5E [299, 300]. Mutations in ARL13B, a small GTPase that forms a molecular complex with INPP5E [284, 294, 296], have also been implicated in Joubert's syndrome, as have mutations in PDE6D, a protein that binds the membrane-targeting prenyl groups of INPP5E [284, 301]. The related ciliopathy MORM is also due to loss of INPP5E function, although in this autosomal recessive disorder the mutation results in a truncated protein that nevertheless retains PIP phosphatase activity [302] but is no longer correctly targeted to the ciliary axoneme. PI3K signalling is required for the development of primary cilia [150] and current evidence suggests that INPP5E functions in the stabilisation of primary cilia as opposed to cilliogenesis [299]. These recent findings reveal a key role for the INPP5E signalling interactome in maintaining ciliar functionality and this is somewhat reminiscent of the situation in OCRL (another PIP-dependent ciliopathy) where mutations affecting molecular interactions in addition to catalytic activity can cause disease. Hence, the loss of INPP5E function and resulting 5-phosphorylated PIP

homeostasis tend to cause developmental abnormalities that are deleterious for the developing nervous system.

6.0 The emerging story of PIPs in Alzheimer's disease

There is now a wealth of evidence implicating PIPs as potential biomarkers and as drug targets in Alzheimer's disease. One of the most high-profile developments in this area has been the discovery that PI is one of only 10 serum lipids that can accurately predict memory loss in up to 90% of cases, 2 years before the onset of dementia symptoms [303]. However, it is not clear yet whether raised serum PI reflects any particular change in PIP metabolism and indeed, the authors concluded that alongside the other biomolecules identified in their lipidomic screen, raised serum PI probably reports increased cell membrane breakdown. However, there are a number of observations that make the case for PIP involvement in Alzheimer's disease. These are:

1. The enrichment of PIP-metabolising enzymes such as PTEN [304] and lipids such as PI(4,5)P_2 [305] in neurofibrillary tangles.

2. Alterations to PIP abundance and metabolism in diseased brains [304, 306-315].

3. Alterations to the catalytic activity of PIP-metabolising enzymes such as synaptojanin [316] and PI4K2A [317, 318], by binding of amyloid β (Aβ) peptides and conversely, the stimulation of Aβ processing enzymes such as the γ-secretase complex by PIPs with particular acyl chains [319]. These results point to the existence of reciprocal product-feedback loops on endosomal membranes that facilitate the cross-regulation of enzymes involved in PIP synthesis and amyloid processing. To further support this hypothesis, there is published evidence of a close correlation between cellular PI(4,5)P_2 and 42-residue Aβ levels [308].

4. Genetic polymorphisms or mutations in genes encoding for PIP-utilising or interacting proteins such as *PICALM, INPP5D* and *SYNJ1* predispose to Alzheimer's disease [320-329]. These genes encode for phosphatidylinositol binding clathrin assembly protein (PICALM) [320-323, 330-334], which contains an N-terminal ANTH domain that binds $PI(4,5)P_2$ [335, 336] and can simultaneously bind clathrin by means of a clathrin-binding motif; the $PI(4,5)P_2$ 5-phosphatase synaptojanin 1 [326, 328, 337], which is required for clathrin-mediated endocytosis [338]; and INPP5D, more commonly known as SHIP1 [339], which like PTEN is a PIP 3-phosphatase that preferentially dephosphorylates $PI(3,4,5)P_3$ to $PI(4,5)P_2$. Most recent evidence indicates that alterations to PICALM functioning leads to defects in autophagy and, in turn, this leads to the accumulation of tau, a process important for the development of Alzheimer's disease [333]. While in Down's syndrome, trisomy 21 results in increased *SYNJ1* gene copy number. This genomic change causes increased expression of synaoptojanin-1 leading to decreased membrane $PI(4,5)P_2$ levels and consequently endosomal trafficking defects [326]. This PIP defect is associated with concomitant reductions in Aβ trafficking and clearance and, in this way, may contribute to the development of early-onset Alzheimer's disease, which is common in Down's syndrome [328, 340].

5. PI4P production by the endosomally localised PI kinase PI4K2A is stimulated by ginsenoside, a naturally occurring molecule that promotes Aβ clearance in the brain of a murine Alzheimer's model [341]. This effect may relate to cholesterol modulation of PI4K2A activity and its palmitoylation-dependent targeting to raft-like intracellular domains [27, 43-45, 48]. This may be further evidence that upregulating intracellular PIP production could be an effective means of countering abrogated Aβ clearance.

6. A recent study has found increased neuronal levels of the PI(3,4,5)P_3-activated protein kinase PDK1 both in Alzheimer's and prion disease brains. This results in increased internalisation, through the caveolar route, of tumour necrosis factor-α-converting enzyme (TACE) receptor and subsequently reduced TACE-mediated α-secretase activity at the cell surface [342]. Consequently, there is decreased proteolysis of both amyloid precursor and prion proteins and this leads to their aberrant accumulation. There is also a report that PDK1 is required for Aβ-mediated cell death [343]. These recent publications provide further evidence that PIP regulation of membrane trafficking pathways exert large effects on neuronal Aβ levels. Similarly, the expression VPS34 (PIK3C3), an endosomal PI3K that synthesises PI3P, is reduced in the brains of Alzheimer's patients and this leads to enhanced processing and reduced sorting of amyloid precursor protein through a mechanism involving ubiquitin-mediated trafficking and the PI3P-binding endosomal sorting complexes required for transport (ESCRT) components Hrs and Tsg101 [344]. VPS34 is widely expressed in the brain and its targeted ablation results in pronounced neurodegeneration and synaptic loss [345]. These combined insights suggest that PIP control of amyloid protein processing is an important process to understand as defects in these pathways are likely to cumulatively lead to amyloid plaque formation in the brain.

6.1 Synaptojanin: a PIP link between Alzheimer's and Parkinson's diseases and epilepsy?

The involvement of synaptojanin in Alzheimer's is worth further comment since mutations in SYNJ1 have been identified in a rare familial version of Parkinson's disease [346-348] and also in an inherited form of Parkinson's associated with epilepsy [349]. A separate study also reported a synaptojanin mutation in an inherited form of epilepsy, suggesting that SYNJ1 mutations can have heterogeneous effects on neuronal function that are not necessarily limited to classical Alzheimer's and Parkinson's symptoms [350, 351]. However, whilst Alzheimer's may represent a gain of function in synaptojanin due to trisomy 21, the mutations associated with Parkinson's disease and epilepsy

are loss of function point mutations in the SAC1 catalytic domain that should have the opposite effect on membrane composition and induce PI(4,5)P_2 accumulation. Interestingly, lipidomic analysis of lipid raft composition in both early stage and incidental Parkinson's patients revealed an increase in phosphatidylinositol levels, which is further evidence that PIP metabolism may be altered in this condition [352, 353]. Hence, it is possible that both Parkinson's and Alzheimer's, although affecting different brain regions and with different symptoms, are to some extent pathological manifestations of reciprocal PIP imbalances within the CNS. Moreover, PI4K2A modulation by cholesterol and ginsenoside point to a possible underappreciated role for PI4P levels in this equation and indicate that an impaired of balance of PI4P and PI(4,5)P_2 binding partners may contribute towards the development of these neurological pathologies.

It is worth noting that genetic mutations in synaptojanin 2 have not been found to cause Parkinson's or Alzheimer's disease. In terms of primary structure, the 2 synaptojanin isoforms are most divergent in their C-termini, with synaptojanin 2 containing a proline-rich region that is absent in synaptojanin 1, even though both proteins are thought to function in clathrin-mediated endocytosis. The *SYNJ2* gene has gained some interest due to its potential role in maintaining cognitive ability and mental health in old age [354, 355], and also because a catalytically inactivating point mutation in this gene in the Mozart mouse strain leads to deafness caused by hair cell loss [356]. Since both synaptojanin proteins have similar PIP substrate specificities it may be the case that, as with the OCRL phosphatases, alterations to the membrane protein interactome in addition to lipid phosphatase activity may be an understudied determinant of how mutations in the D5 phosphatases can give rise to such a heterogeneous range of neurological defects.

It is important to point out that other branches of the PIP signalling pathway are likely to be important in Parkinson's disease. Particularly relevant in this regard is the mitochondrial protein PINK1 (phosphatase and tensin [PTEN] homologue-induced putative kinase 1), which is a downstream phosphorylation substrate of Akt and has been found to be mutated in a particular

early-onset inherited form of this neurodegenerative disorder [357-360]. In concordance with this, there is evidence that D2 dopamine receptor signalling via PI3K is anti-apoptotic and thus potentially neuroprotective in Parkinson's disease [361].

7.0 PIPs in stroke, exocitotoxic cell death and cerebral ischaemia

While PIPs have many roles in inherited neuropathies, overgrowth syndromes and neurodegenerative disorders, there are also demonstrations that these lipids are important for CNS cell survival following the ischaemic trauma caused by a cerebral haemorrhage (stroke). Excitotoxic cell death due to augmented glutamate stimulation of NMDA receptors and Ca^{2+} dyshomeostasis is a common consequence in this type of brain injury and PIPs, in particular $PI(3,4,5)P_3$, have been implicated in this neuropathological process [362].

PIP levels, which are contingent on lipid kinase activity, ATP production and thus mitochondrial function, are known to decrease following periods of cerebral ischaemia [363-366]. Furthermore, there are strong indications from murine genetic models that PI4P production is important for the survival of particular cell populations in the CNS [18, 367]. In a rat model for transient forebrain ischaemia, PI4KA expression was found to be heavily downregulated, specifically in CA1 pyramidal neurons, as was its upstream lipid product $PI(4,5)P_2$ [367]. This change in PIP metabolism correlated with increased neuronal apoptosis and was found to be reversible in cultured cell lines by re-expression of catalytically active PI4KA [367]. These results are consistent with the idea that PI4P synthesis has anti-apoptotic functions in the brain [18]. However, most of the evidence for PIP involvement in cerebral trauma concerns a neuroprotective function for pro-survival PI3K and Akt signalling pathways [151, 368-376]. However, there is one report that PI3K activity has the opposite effect and promotes neuronal oxidative stress through $PI(3,4,5)P_3$-dependent neuronal NADPH oxidase activation [369]. Some of the most unexpected findings in this arena have emanated from studies focused on identifying serum biomarkers from stroke patients. In one such study, an

unbiased proteomic screen found that an increased serum level of the PI(3,4,5)P_3 phosphatase SHIP-1 accurately predicted acute ischaemic stroke [377], whilst another found that anti-PI antibodies were prevalent in a group of young stroke patients [378]. These findings are difficult to rationalise based on any known disease mechanism and require validation in a larger patient cohort. Nevertheless, when viewed together with the demonstration that raised serum PI is an accurate biomarker for Alzheimer's disease [303], there appears to be an emerging trend for PIP pathway molecules, which are not normally secreted at high levels, to be elevated in the serum of patients with severe neurological diseases. However, further work is needed to clarify the mechanisms that underlie these phenomena and also to probe the general applicability of these findings to other CNS disorders.

8.0 Conclusions

PIPs are involved in more or less every type of neurological disease, from rare and often devastating genetic diseases to more common neurodegenerative conditions such as Alzheimer's that are becoming more widespread as life expectancy increases (Table 1). There has been substantial progress, particularly in the last 5 years, in understanding how PIP pathways mediate a range of physiological functions in the CNS and how genetic mutations affecting these pathways can lead to neurological diseases. However, with the notable exceptions of glioma, multiple sclerosis and to some extent Alzheimer's disease, there has been less progress in translating this new knowledge into possible new treatments. Some of these problems are simply down to the fact that this information is novel and it will take some time and financial investment in order to generate, for example, small molecule inhibitors that are both isoform specific and blood-brain barrier permeable. Another issue is the complexity of the neurobiology regulated by the PIP lipids and the presence of compensatory and redundant biochemical pathways that could potentially confer resistance to targeted therapies. Even if treatment strategies remain challenging, it is fair to conclude that biomolecules associated with these pathways may be useful biomarkers for predicting, diagnosing

and classifying neurological conditions and also for discovering molecular connections between diseases that could inform future treatment strategies.

Legends

Table 1.

List of neurological diseases summarising the proteins, enzymes and PIP species involved.

Figure 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.

Figure 2.

The structures of PI, PI4P and PI(4,5)P_2. A schematic diagram illustrating the molecular structures of the most abundant brain PIPs. The molecular species shown here are of the 1-stearoyl, 2-arachidonoyl varieties which are the common acyl chain additions found in PIPs from the CNS. The hydrophobic acyl chains anchor the PIPs in the membrane while the hydrophilic inositol headgroup. is exposed to the cytosol. Note that the charge differences between the different PIPs arise from single phosphorylation and dephosphorylation events on the inositol head group moiety and that these changes are due to the catalytic activities of phosphoinositide kinase and phosphatase enzymes. Imbalances in the ratio of PI4P:PI(4,5)P_2 may be important in both Lowe's & Dent's syndromes, Alzheimer's & Parkinson's diseases. Several inherited conditions with neurological involvement including Andersen-Tawil syndrome and a dominant intermediate presentation of Charcot Marie Tooth neuropathy are caused by mutations that abolish protein binding to PI(4,5)P_2.

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Table

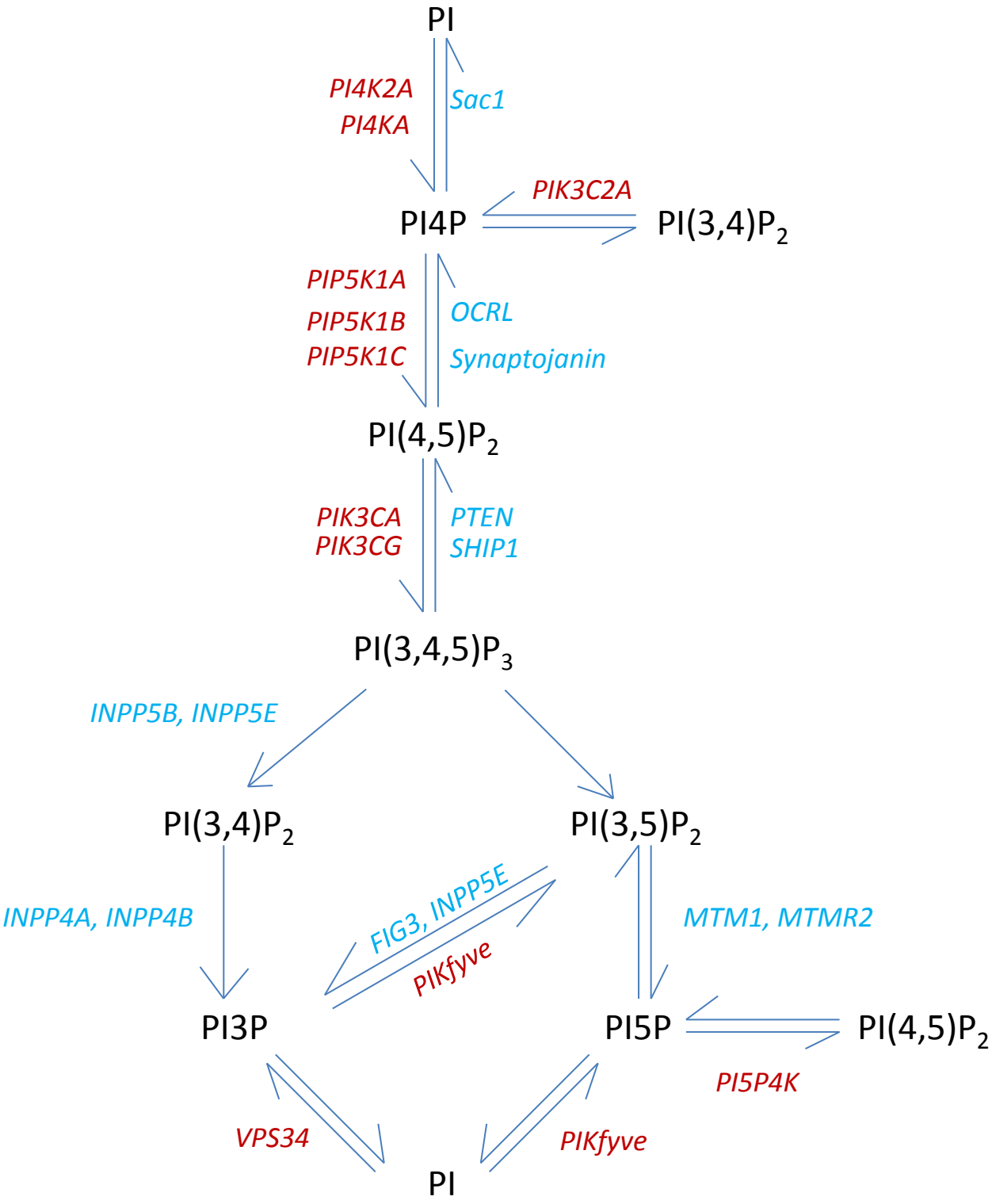
Table 1

Disease	Protein	Lipid
PI(4,5)P_2 imbalances		
Chronic pain	PIPK5K1C	PI(4,5)P_2
	PLCB3	PI(4,5)P_2
Friedreich's ataxia	PIP5K1B	PI(4,5)P_2
Lethal muscle contractural syndrome type 3	PIPK5K1C	PI(4,5)P_2
Charcot-Marie-Tooth disease (intermediate form *and* CMT2B)	Dynamin	PI(4,5)P_2
OCRL Lowe's disease	OCRL1	PI(4,5)P_2
Dent's disease	OCRL1	PI(4,5)P_2
Channelopathies		
Epilepsy	KNVQ channel	PI(4,5)P_2
Andersen-Tawil syndrome	KCNJ2 channel	PI(4,5)P_2
Charcot-Marie-Tooth type 2C	TRPV4 channel	PI(4,5)P_2
Mucolipidosis type IV	TRPML1 channel	PI(3,5)P_2
Defective PI3K pathways		
Multiple sclerosis	PIK3G	PI(3,4,5)P_3
Hemimegalencephaly	PIK3CA	PI(3,4,5)P_3
	AKT3	PI(3,4,5)P_3
Megalencephaly	PIK3R2	PI(3,4,5)P_3
	PIK3CA	PI(3,4,5)P_3
	PTEN	PI(3,4,5)P_3
	AKT3	PI(3,4,5)P_3
Microcephaly	INPP4A	PI(3,4)P_2
PTEN hamartoma tumour syndromes (PHTS)	PTEN	PI(3,4,5)P_3
Brain cancers	PTEN	PI(3,4,5)P_3
	PIK3CA	PI(3,4,5)P_3
X-linked recessive centronuclear myopathy	MTM1	PI(3,5)P_2
CMT4B2	MTMR2	PI(3,5)P_2
CMT4J	Sac3/FIG4	PI(3,5)P_2

Table 1

Yunis-Varón syndrome	Sac3/FIG4	$PI(3,5)P_2$
Amytropic lateral sclerosis	Sac3/FIG4	$PI(3,5)P_2$
Joubert's ciliopathy	INPP5E	$PI(3,5)P_2$ /$PI(3,4,5)P_3$
MORM ciliopathy	INPP5E	$PI(3,5)P_2$ /$PI(3,4,5)P_3$
Autism spectrum	PTEN	$PI(3,4,5)P_3$
	PIK3CA	$PI(3,4,5)P_3$
	PIK3C2A	$PI(3,4)P_2$
	PIK3R2	$PI(3,4,5)P_3$
Alzheimer's and Parkinson's diseases		
Alzheimer's disease	PICALM	
	PI4K2A	PI4P
	Synaptojanin 1	$PI(4,5)P_2$
	PDK1	$PI(3,4,5)P_3$
	VPS34	PI3P
Parkinson's disease	Synaptojanin 2	$PI(4,5)P_2$

Figure 1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PI4P
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PIP5K1B
PIP5K1C
OCRL
Synaptojanin
PI(4,5)P2
PIK3CA
PIK3CG
PTEN
SHIP1
PI(3,4,5)P3
INPP5B, INPP5E
PI(3,4)P2
PI(3,5)P2
INPP4A, INPP4B
FIG3, INPP5E
PIKfyve
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PI5P
PI(4,5)P2
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VPS34
PIKfyve
PI

Figure
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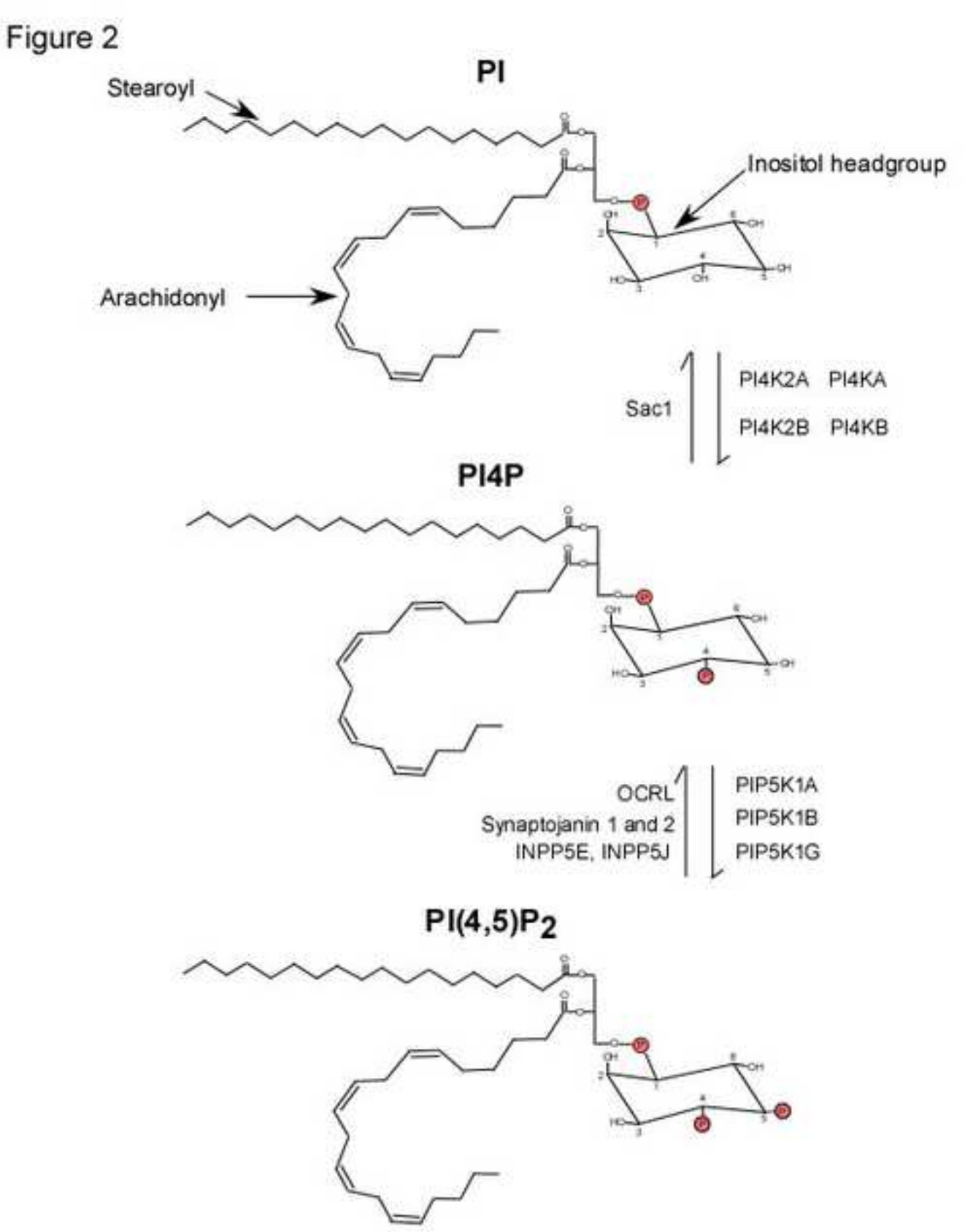

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