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Chapter

Vitamin B6 and Related Inborn Errors of Metabolism

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Abstract

Vitamin B6 (vitB6) is a generic term that comprises six interconvertible pyridine compounds. These vitB6 compounds (also called vitamers) are pyridoxine (PN), pyridoxamine (PM), pyridoxal (PL) and their 5′-phosphorylated forms pyridoxine 5′-phosphate (PNP), pyridoxamine 5′-phosphate (PMP) and pyridoxal 5′-phosphate (PLP). VitB6 is an essential nutrient for all living organisms, but only microorganisms and plants can carry out *de novo* synthesis of this vitamin. Other organisms obtain vitB6 from dietary sources and interconvert its different forms according to their needs via a biochemical pathway known as the salvage pathway. PLP is the biologically active form of vitB6 which is important for maintaining the biochemical homeostasis of the body. In the human body, PLP serves as a cofactor for more than 140 enzymatic reactions, mainly associated with synthesis, degradation and interconversion of amino acids and neurotransmitter metabolism. PLP-dependent enzymes are also involved in various physiological processes, including biologically active amine biosynthesis, lipid metabolism, heme synthesis, nucleic acid synthesis, protein and polyamine synthesis and several other metabolic pathways. PLP is an important vitamer for normal brain function since it is required as a coenzyme for the synthesis of several neurotransmitters including D-serine, D-aspartate, L-glutamate, glycine, γ-aminobutyric acid (GABA), serotonin, epinephrine, norepinephrine, histamine and dopamine. Intracellular levels of PLP are tightly regulated and conditions that disrupt this homeostatic regulation can cause disease. In humans, genetic and dietary (intake of high doses of vitB6) conditions leading to increase in PLP levels is known to cause motor and sensory neuropathies. Deficiency of PLP in the cell is also implicated in several diseases, the most notable example of which are the vitB6-dependent epileptic encephalopathies. VitB6-dependent epileptic encephalopathies (B6EEs) are a clinically and genetically heterogeneous group of rare inherited metabolic disorders. These debilitating conditions are characterized by recurrent seizures in the prenatal, neonatal, or postnatal period, which are typically resistant to conventional anticonvulsant treatment but are well-controlled by the administration of PN or PLP. In addition to seizures, children affected with B6EEs may also suffer from developmental and/or intellectual disabilities, along with structural brain abnormalities. Five main types of B6EEs are known to date, these are: PN-dependent epilepsy due to ALDH7A1 (antiquitin) deficiency (PDE-ALDH7A1) (MIM: 266100), hyperprolinemia type 2 (MIM: 239500), PLP-dependent epilepsy due to PNPO deficiency (MIM: 610090), hypophosphatasia (MIM: 241500) and PLPBP deficiency (MIM: 617290). This chapter provides a review of vitB6 and its different vitamers, their absorption and

metabolic pathways in the human body, the diverse physiological roles of vitB6, PLP homeostasis and its importance for human health. Finally, the chapter reviews the inherited neurological disorders affecting PLP homeostasis with a special focus on vitB6-dependent epileptic encephalopathies (B6EEs), their different subtypes, the pathophysiological mechanism underlying each type, clinical and biochemical features and current treatment strategies.

Keywords: vitamin B6 (vitB6), Salvage pathway, PLP-dependent enzymes, inherited vitB6-dependent epilepsies

1. Introduction

Vitamin B6 (vitB6) is a generic term that refers to a group of six interconvertible chemical compounds that share a pyridine ring in their centre. These vitB6 compounds (also called vitamers) are pyridoxine (PN), pyridoxamine (PM), pyridoxal (PL) and their 5′-phosphorylated forms pyridoxine 5′-phosphate (PNP), pyridoxamine 5′-phosphate (PMP) and pyridoxal 5′-phosphate PLP) [1] (**Figure 1**). VitB6 is required by all living organisms for their survival, but only microorganisms and plants can carry out *de novo* synthesis of this vitamin. Other organisms including humans acquire vitB6 from exogenous sources and interconvert its different forms according to their needs using a biochemical pathway known as the salvage pathway [1, 3].

1.1 Metabolism of vitB6

Among the six vitB6 compounds, PLP is the biologically active and most important vitamer since it is required as a cofactor for a multitude of enzymes in the body. Humans and other mammals obtain PLP directly from diet or through synthesis from other vitameric forms ingested with food or recycled from degraded PLP-dependent enzymes via the salvage pathway [1, 4] (**Figure 2**). The central enzyme in this pathway is PNP oxidase (PNPO), a flavin mononucleotide (FMN)-dependent enzyme that is capable of converting PNP or PMP to the active cofactor

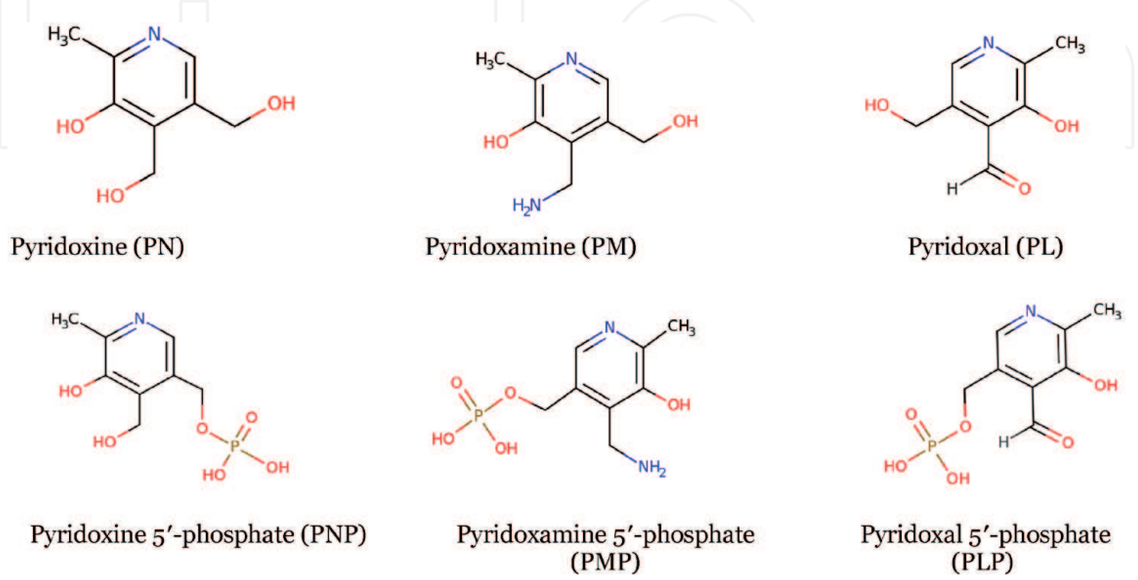


Figure 1.
Chemical structures of the six vitamin B6 vitamers. Colored atoms designate oxygen or hydroxyl group (red), nitrogen or amine group (blue) and phosphorus (brown). (Retrieved from [2]).

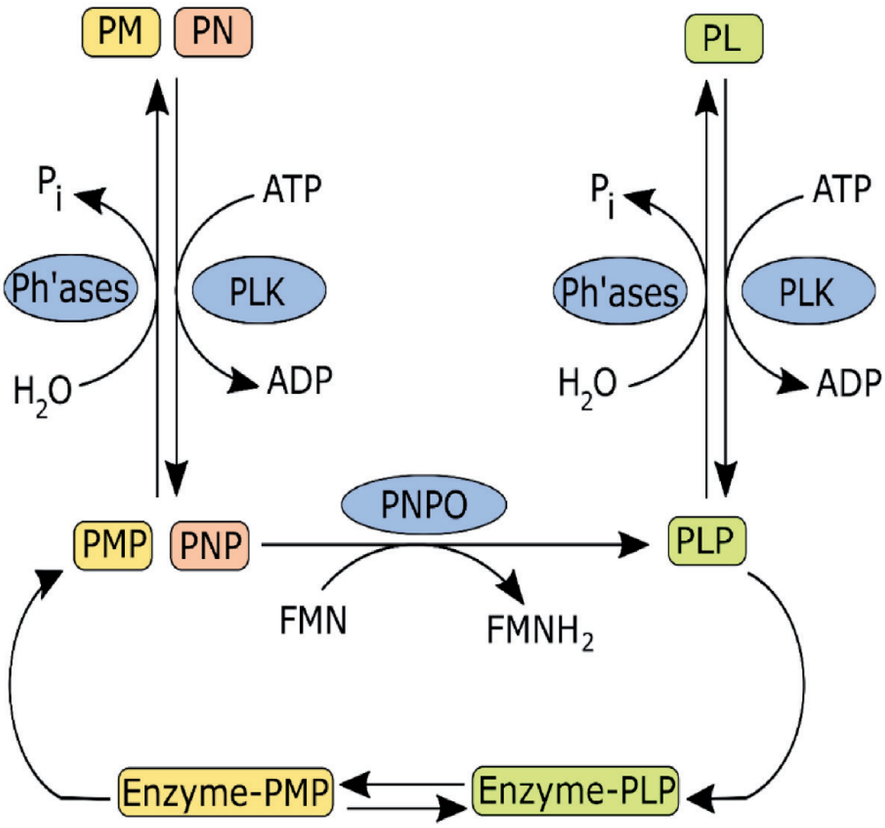


Figure 2.
The PLP salvage pathway. Phosphorylated vitamers are converted to PLP by the enzyme PNPO. PLP is also recycled from degraded holo-B6 enzymes through PMP as an intermediate step. ADP: adenosine diphosphate, ATP: adenosine triphosphate, $FMNH_2$: flavin mononucleotide reduced form, Ph'ases: phosphatases, Pi: inorganic phosphate. (Based on [5–7]).

PLP [1]. Other important enzymes in the salvage pathway are PL kinase (PLK) and a number of different phosphatases [5].

VitB6 vitamers are widely available in animal and plant food sources. PLP and in a lesser amount, PMP are present as such in animal-derived foods, mainly associated with muscle glycogen phosphorylase, while plant foods are more enriched in PN, PNP and PN glucosides [1, 4, 8].

After being ingested, phosphorylated vitamers (PLP, PNP and PMP) undergo dephosphorylation by the ecto-enzyme tissue-specific intestinal phosphatase (IP) [5], whereas PN glucoside (PNG) vitamers from plants are hydrolyzed by a glucosidase before absorption [1, 10]. Absorbed vitamers are carried by the portal circulation to the liver where they are phosphorylated by PLK [5]. Inside liver cells, PNP and PMP are oxidized by PNPO to form PLP, which is then released to the circulation bound to lysine-190 residue of albumin (**Figure 3**) [9–11]. Binding of PLP to albumin is thought to protect the cofactor from hydrolysis and other reactions [11]. About 60% of circulating vitB6 is in the form of albumin-bound PLP, while PN, PM and PL constitutes the remaining proportion [5].

Prior to delivering the circulating PLP to different tissues, it is dephosphorylated to PL by the ecto-enzyme tissue nonspecific alkaline phosphatase (TNSALP) to enable entry into the cells and through the blood–brain barrier. Inside the cell, PL is re-converted by PLK to PLP, which now can be used as a cofactor in many biochemical reactions (**Figure 3**) [1, 5, 9]. Degradation of PLP-bound enzymes (holo-B6 enzymes) can generate PMP, which is then oxidized back to PLP by the action of PNPO [6] (**Figures 2** and **3**).

Besides the liver, it has been shown that the intestine also contributes an important role in vitB6 metabolism. *In vitro* studies utilizing human intestinal

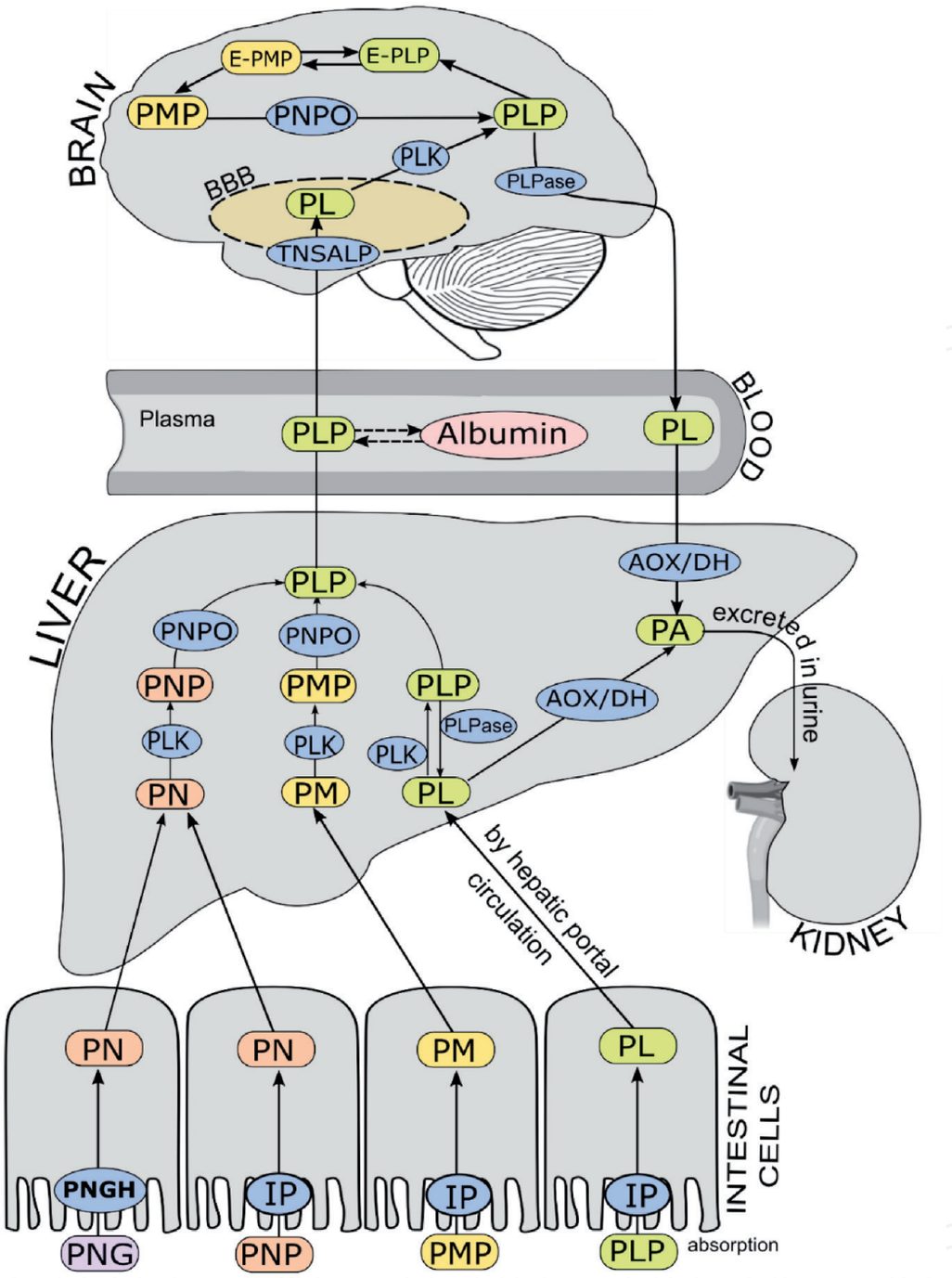


Figure 3.
Metabolism of vitB6 vitamers in different tissues of the body. PNGH: PNG hydrolase; PLPase: PLP phosphatase; AOX/DH: aldehyde oxidase/dehydrogenase; BBB: blood–brain barrier; PA: pyridoxic acid; E-PLP: enzyme-bound PLP; E-PMP: enzyme-bound PMP. (Based on [6, 7]).

epithelial Caco-2 cells [12] demonstrated that, after incubation of these cells with multiple vitB6 vitamers, PL was the only vitamer detected at the basolateral side which indicated that all other vitamers were converted to PL inside the intestinal cells. Excretion of PN and PM at the basolateral side was only detected when the enterocytes were incubated with high concentrations of these vitamers. The authors suggested that under normal dietary intakes, PN and PM are converted to PL by the enterocytes and PL becomes the principal vitamer that reaches the portal circulation. All other organs including the liver can then obtain PL from the circulation and only require PLK to produce PLP. Under high vitB6 intakes, however, the ingested amounts of PN or PM may surpass the intestine's capacity to fully metabolize these vitamers. In this case, PN and PM will be released to the

portal circulation and will subsequently be converted to PLP in the liver. The study also showed the expression of a full battery of the salvage enzymes in Caco-2 cells as well as in lysates of human intestine, adding further evidence for a major role of the intestine in vitB6 metabolism [12]. Earlier works in mice [13, 14] have also pointed to a similar role of the intestine. In these studies, following oral administration of radiolabeled PN, labeled PL and PLP were detected in the mouse intestine and portal circulation indicating involvement of the intestine in converting dietary vitamers to circulating PL [13, 14].

1.2 Catabolism of vitamin B6

At the other end of vitB6 metabolism, little is known about the catabolic pathways in humans or other mammals. In contrast, these mechanisms are well established in microorganisms [3, 11, 15]. In humans and other mammals, the primary product of the degradation of PLP (and all other vitB6 vitamers) is 4-pyridoxic acid (4-PA). This compound, which is excreted in urine, is generated in two steps. In the first one, PLP is hydrolyzed to PL by the action of an intracellular enzyme known as PLP phosphatase (PLPase). In the following step, PL is oxidized to 4-PA by a non-specific aldehyde oxidase (AOX) or aldehyde dehydrogenase (**Figure 3**) [3, 6, 12, 15, 16]. In microorganisms, 4-PA is further degraded to other metabolites that can be utilized by the cell in various biochemical processes [15]. Some microbial vitB6 catabolic products such as 5-pyridoxic acid (5-PA), 5-pyridoxolactone [17] and 4-pyridoxolactone [17, 18] have been also discovered in human individuals under consumption of high amounts of vitB6. Several other PN derivatives have been identified in humans and/or other mammalian species, but their biochemical pathways and precise functions have not yet been unraveled.

For example, Coburn and Mahuren [19] detected pyridoxine 3-sulfate, pyridoxal 3-sulfate and *N*-methylpyridoxine in the urine of domestic cats, and, interestingly, these chemicals were excreted at concentrations higher than 4-PA, even with moderate intake of PN. Other studies reported the discovery of multiple PM derivatives in urine samples from PM-administered diabetic and obese rats [20, 21]. Moreover, at least nine unidentified vitB6 metabolites were detected in human urine after oral administration of radiolabeled PN [17, 19].

Oxidation of PN at the 5′ position, followed by sequential dehydrogenation to form 5-PA, is known to exist only in the PN catabolic pathway of some bacterial species like *Pseudomonas* IA and *Arthrobacter* Cr-7, where the enzymes catalyzing these reactions have been characterized [15]. Similar reactions have been proposed to occur in mammals based on experimental clues. The first one was provided by the study of Coburn and colleagues [22] who showed that healthy men who ingested a structural analog of PN, 4′-deoxypyridoxine, excreted 4'-Deoxy-5-pyridoxic acid in their urine. A similar experiment was carried out in guinea pigs [23], and the results indicated that these animals were also able to convert 4′-deoxypyridoxine to 4′-deoxy-5-pyridoxic acid. All together, these studies provided evidence for the possible existence of alternative but currently undiscovered catabolic routes of PN in humans and other mammals.

1.3 Vitamin B6 transportation across cellular membrane

Multiple experimental evidence suggests that, as with most water-soluble vitamins [24], the transportation of vitB6 across mammalian cell membrane is carrier-mediated. Studies in cultured human intestinal [12, 25], colonic [26], and renal cells [27] and animal-derived renal proximal tubular cells [28] demonstrated the presence of an efficient and specific carrier-facilitated mechanism for cellular

uptake of vitB6. Such a specific transporting membrane carrier was employed to produce a high affinity gene delivery system into cancer cells using a vitB6-coupled vector [29]. However, the molecular identity of vitB6 transporter protein in mammals has remained elusive [12, 30]. Among eukaryotes, the only vitB6 transporters identified so far are the yeast transporters, Tpn1p [31] and Bsu1 [32], and, recently, PUP1 in plant species *Arabidopsis* (first to be identified in plants) [33].

1.4 Physiological roles of vitamin B6

PLP, the coenzymatically active form of vitamin B6, plays an important role in maintaining the biochemical homeostasis of the body [34]. In the human body, PLP is an essential cofactor for more than 140 distinct enzymatic activities, mainly associated with synthesis, degradation and interconversion of amino acids as well as with neurotransmitter metabolism [35–38]. PLP-dependent enzymes are also involved in a multitude of other cellular processes, including biologically active amine biosynthesis, lipid metabolism, heme synthesis, nucleic acid synthesis, protein and polyamine synthesis and several other metabolic pathways (**Figure 4**) [5, 6]. Furthermore, PLP is important in energy homeostasis through glycogen degradation and gluconeogenesis, since PLP is a cofactor for glycogen phosphorylase and gluconeogenic transaminases [36, 41]. In folate-mediated one-carbon metabolism (FOCM), PLP is required as a cofactor for the enzyme serine hydroxymethyltransferase, both its cytoplasmic (SHMT1) and mitochondrial (SHMT2) isoforms. FOCM is an important pathway that is involved in a number of physiological processes such as DNA methylation, redox homeostasis and purines and thymidine biosynthesis [36, 42].

As a coenzyme for the synthesis of several neurotransmitters including D-serine, D-aspartate, L-glutamate, glycine, γ-aminobutyric acid (GABA),

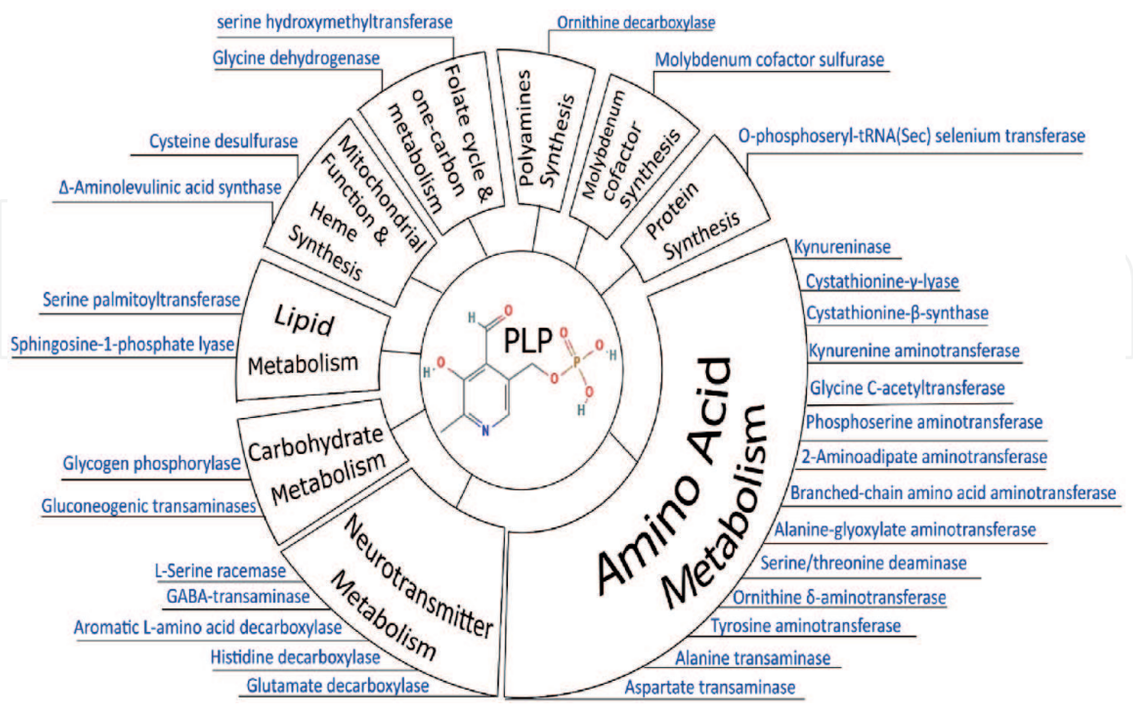


Figure 4.
The diverse cellular functions of PLP. Names in blue are the PLP-dependent enzymes involved in each metabolic process. Some enzymes can be implicated in mutiple processes. An example is branched-chain amino acid aminotransferase which can fall under amino acid and neurotransmitter metabolism. Glycine dehydrogenase can be classified under folate cycle and amino acid and neurotransmitter metabolism. (Based on [6, 39]; PLP chemical structure was retrieved from [40]).

serotonin, epinephrine, norepinephrine, histamine and dopamine, PLP is an important vitamer for normal brain function [5, 43]. For example, GABA, the major inhibitory neurotransmitter in the central nervous system (CNS), is synthesized from L-glutamate by the PLP-dependent enzyme glutamate decarboxylase (GAD). Moreover, PLP is a cofactor for branched-chain amino acid aminotransferase (BCAT) which catalyzes the synthesis of L-glutamate, the major excitatory neurotransmitter, from branched-chain amino acids like leucine and valine [5].

Another important PLP-dependent enzyme in the brain is aromatic L-amino acid decarboxylase (AADC), which catalyzes the final steps in the biosynthetic pathways of serotonin and dopamine (**Figure 5**) [5, 36]. These neurotransmitters also serve as precursors for other important compounds in the brain, specifically melatonin, norepinephrine and epinephrine (**Figure 5**) [5, 46].

In addition to its role as an enzymatic cofactor, PLP has been shown to play a role in preventing DNA damage [47] and in modulating the activity and expression of steroid hormone receptors [6, 48]. vitB6 has also been described as an efficient antioxidant in plants and fungi, with the ability of its different vitamers to quench reactive oxygen species [1, 49, 50].

1.5 PLP homeostasis and its importance for human health

PLP is a highly reactive compound because of its aldehyde group at the 4′ position which can undergo spontaneous complexation with other molecules within the cell [1, 9]. It may bind with amino groups in proteins and disrupt their structure [6]. For example, it has been shown that PLP can react with the lysine residue in the

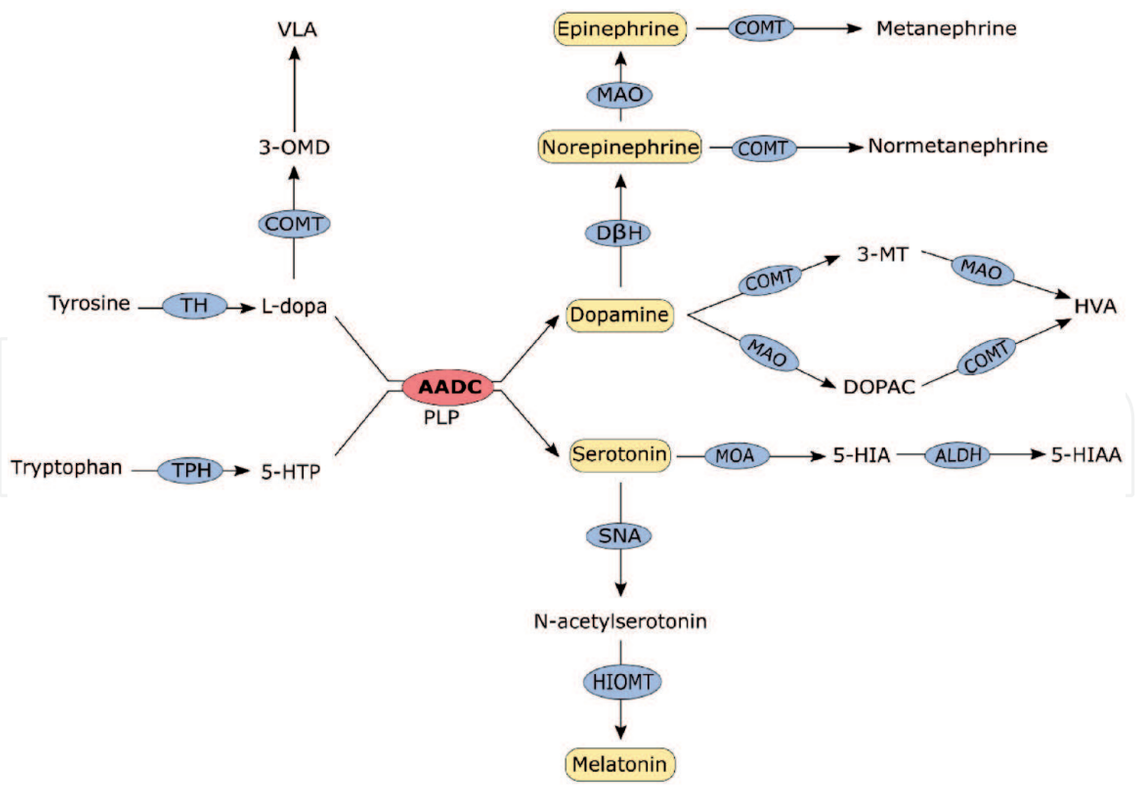


Figure 5.
Biosynthetic pathway for biogenic amine neurotransmitters and melatonin. The PLP-dependent enzyme, AADC, catalyzes a central step in this pathway. TH: tyrosine hydroxylase; TPH: tryptophan hydroxylase; L-dopa: levodopa; 5-HTP: 5-hydroxytryptophan; DβH: dopamine β-hydroxylase; MAO: monoamine oxidase; SNA: serotonin N-acetylase; HIOMT: hydroxyindole O-methyltransferase; COMT: catechol-O-methyltransferase; ALDH: Aldehyde dehydrogenase; 3-OMD: 3-O-methyldopa; VLA: vanillactic acid; 5-HIA: 5-hydroxyindole acetaldehyde; 5-HIAA: 5-hydroxyindoleacetic acid; 3-MT: 3-methoxytyramine; HVA: homovanillic acid; DOPAC: 3,4-dihydroxyphenylacetic acid. (Based on [44, 45]).

active site of human DNA topoisomerase I, causing its inhibition [51, 52]. Through a chemical reaction known as Knoevenagel condensation, PLP can also react with intermediate metabolites like Δ^1-pyrroline 5-carboxylate and Δ^1-piperideine 6-carboxylate, which form the molecular basis of PLP depletion in the neurometabolic diseases ALDH7A1 deficiency and hyperprolinaemia type II, respectively [6]. Because of its high reactivity and to prevent toxic accumulation of this cofactor, the intracellular pool of free PLP is maintained at very low concentration (about 1 μM in eukaryotic cells) [1, 5, 6]. It is therefore likely that PLP production in the cell is tightly regulated [5], and experimental work indicates the presence of an efficient mechanism that maintains intracellular PLP levels within optimum levels [12]. However, how the concentration of PLP is controlled in mammalian tissues is not entirely understood [3, 34].

A number of mechanisms have been proposed that help in PLP homeostasis. First, both enzymes that produce PLP, PLK and PNPO, are inhibited by their product PLP and its rate of synthesis can, therefore, be controlled by this feedback inhibition [1, 5, 6]. Enzymes that degrade PLP and PL, like PLPase and AOX, respectively, have also been proposed as a mechanism that keeps free PLP at low level within the cell [1, 5, 6]. Proteins that are known to naturally bind PLP, like muscle glycogen phosphorylase, plasma albumin and hemoglobin in red blood cells, contribute to reducing the amount of free reactive PLP [6]. In addition to its catalytic role in PLP synthesis, a recent study [53] demonstrated that PNPO forms a tight a binding with PLP at a noncatalytic site *in vitro*. The study further showed that PLP-bound PNPO interacts with several PLP-dependent enzymes and hypothesized that it may serve as a safe carrier of the reactive cofactor to its dependent enzymes [53]. Another more recently proposed PLP carrier protein is known as PLPHP or PLP Homeostasis Protein (*described in detail in Section 2.5*).

Conditions that disrupt cellular PLP homeostasis can cause disease. For example, inactivation of PLPP in mice led to increase in PLP levels, anxiety and motor deficits [54]. In humans, intake of high doses of vitB6 is known to cause motor and sensory neuropathies [1, 5]. Deficiency of PLP in the cell is also implicated in several pathologies, most notably the so-called vitB6-dependent epileptic encephalopathies [1, 5, 9, 37].

2. VitB6-dependent epileptic encephalopathies

VitB6-dependent epileptic encephalopathies (B6EEs) represent a clinically and genetically heterogeneous group of rare inherited metabolic diseases [55, 56]. These debilitating conditions are characterized by recurrent seizures in the prenatal, neonatal, or postnatal period, which are typically resistant to conventional anticonvulsant treatment but well-controlled by the administration of PN or PLP [56–59]. In addition to seizures, children affected with B6EEs may also suffer from developmental and/or intellectual disabilities, along with structural brain abnormalities [60]. The 5 principal types of B6EEs: PN-dependent epilepsy due to ALDH7A1 (antiquitin) deficiency (PDE-ALDH7A1) (MIM: 266100), hyperprolinemia type 2 (MIM: 239500), PLP-dependent epilepsy due to PNPO deficiency (MIM: 610090), hypophosphatasia (MIM: 241500) and PLPBP deficiency (MIM: 617290) [6, 9, 60, 61] (**Table 1**). According to the underlying pathobiochemical mechanism, these forms of B6EEs can be categorized into: 1) defects in amino acid catabolic pathways causing buildup of byproducts that react with PLP (PDE-ALDH7A1 and hyperprolinemia type 2), 2) defects in the vitB6 salvage pathway (PNPO deficiency), and 3) defects in cellular uptake of PLP (hypophosphatasia) [6, 9] (**Table 1**). In the most

Disease name	PN-dependent epilepsy (PDE-ALDH7A1)	PLP-dependent epilepsy	Hyperprolinemia type 2	Hypophosphatasia	PLPBP deficiency
Affected gene	*ALDH7A1*	*PNPO*	*ALDH4A1*	*ALPL*	*PLPBP*
Affected enzyme or protein/pathway(s)	α-AASA dehydrogenase/ lysine catabolism pathway	PNP oxidase/vitB6 salvage pathway	P5C dehydrogenase/Proline catabolism pathway	TNSALP/Extracellular dephosphorylation of PLP, Bone mineralization	PLPHP/PLP homeostasis
Pathophysiological mechanism of PLP deficiency	Accumulating lysine metabolite, P6C, reacts with and inactivates PLP	PNPO is required for intracellular production of PLP from PNP/PMP	Accumulating proline metabolite, P5C, reacts with and inactivates PLP	TNSALP is required for extracellular conversion of PLP to PL to enable its cellular uptake	PLPHP is required for maintaining cellular PLP homeostasis
Main clinical features	Neonatal seizures, DD/ID	Neonatal seizures, DD/ ID	Infantile seizures, DD/ID, ataxia	Rickets, Osteomalacia, Neonatal seizures	Neonatal seizures, DD/ID
Biomarkers (biofluid)	High α-AASA (U/P), P6C (P), PIP (P)	High PM, PM/PA ratio (P)	High proline (P), P5C (U)	Low ALP (P), high PLP (P), high PEA (U)	No specific biomarker
Commonly used vitB6 treatment	PN	PLP	PN	PN	PN
References	[9, 60, 62]	[9, 57, 63]	[6, 60, 63, 64]	[9, 60, 65, 66]	[7, 67, 68]

Abbreviations: α-AASA: α-aminoadipic semialdehyde; P6C: Δ^1-piperideine-6-carboxylic acid; DD: developmental delay; ID: intellectual disability; U: urine; P: plasma; PIP: pipecolic acid; P5C: pyrroline 5-carboxylic acid; ALP: alkaline phosphatase; PEA: phosphatidylethanolamine GPI: glycosyl phosphatidylinositol.

Table 1.
Summary of the genetic, biochemical and clinical features of B6EEs.

recently discovered type, PLPBP deficiency, the exact mechanism that disrupts PLP homeostasis is not fully understood [7].

2.1 PN-dependent epilepsy (ALDH7A1 deficiency)

2.1.1 Disease mechanism

PN-dependent epilepsy (PDE-ALDH7A1) is caused by homozygous or compound heterozygous mutations in the *ALDH7A1* gene (also known as antiquitin, ATQ). *ALDH7A1* codes for α-aminoadipic semialdehyde dehydrogenase, an enzyme that functions within the lysine catabolism pathway in the brain and peripheral tissues [62]. In PDE-ALDH7A1, loss of the enzyme's function leads to the accumulation of three upstream lysine catabolites: Δ^1-piperideine-6-carboxylic acid (P6C), α-aminoadipic semialdehyde (α-AASA) and pipecolic acid (PIP) [60] (**Figure 6**). Through a chemical reaction known as Knoevenagel condensation, accumulating P6C spontaneously conjugates with PLP, forming inactive complex products and causing cellular deficiency of this important cofactor [62] (**Figure 6**). Seizures are thought to occur because PLP is required for neurotransmitter metabolism, particularly for the synthesis of GABA from glutamate [71].

2.1.2 Clinical features

The main clinical manifestation of PDE-ALDH7A1 is recurrent perinatal-onset seizures that are resistant to conventional anticonvulsant treatment, but which show remarkable response to the administration of high doses of PN [60, 72]. Seizures usually relapse when PN treatment is discontinued, either incidentally or for diagnostic purposes [60]. In some cases, the mother of an affected child has described abnormal fetal movements during pregnancy, suggestive of pre-natal onset of seizures [55, 73–75]. In atypical cases, seizure onset can be delayed to up to 3 years of age [60], and in one exceptional case, Srinivasaraghavan et al. [76] reported an Indian female with genetically proven PDE-ALDH7A1 in whom seizures did not start until the age of 17 years (juvenile onset).

In addition to seizures, most PDE-ALDH7A1 patients (about 75%) also suffer from developmental delay and moderate to severe intellectual disability [60, 72, 77]. In addition, as revealed by neuroimaging analysis, a spectrum of structural brain defects have been described in affected children with anomalies of corpus callosum (agenesis/hypoplasia/dysplasia) and white matter being common features [75, 77–79]. Motor deficits (hypotonia/hypertonia/dystonia), irritability, autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD) and anxiety are additional features reported in patients [75, 77, 80].

The phenotypic spectrum of PDE-ALDH7A1 may also include non-neuronal features, but these are less frequently observed in patients. Reported examples are ocular problems, hypoglycemia, hypothyroidism, lactic acidosis, profound electrolyte disturbances, diabetes insipidus, coagulopathy, anemia, respiratory distress and hypotension [60, 77, 79, 81, 82].

2.1.3 Biochemical features and diagnostic biomarkers

In PDE-ALDH7A1, blockade of the ATQ-catalyzed step in the lysine catabolism pathway leads to accumulation of 3 upstream metabolites, P6C, α-AASA and PIP, as discovered by screening of patients' body fluids. Presence of these metabolites in supraphysiological levels is considered the hallmark biochemical feature of ATQ

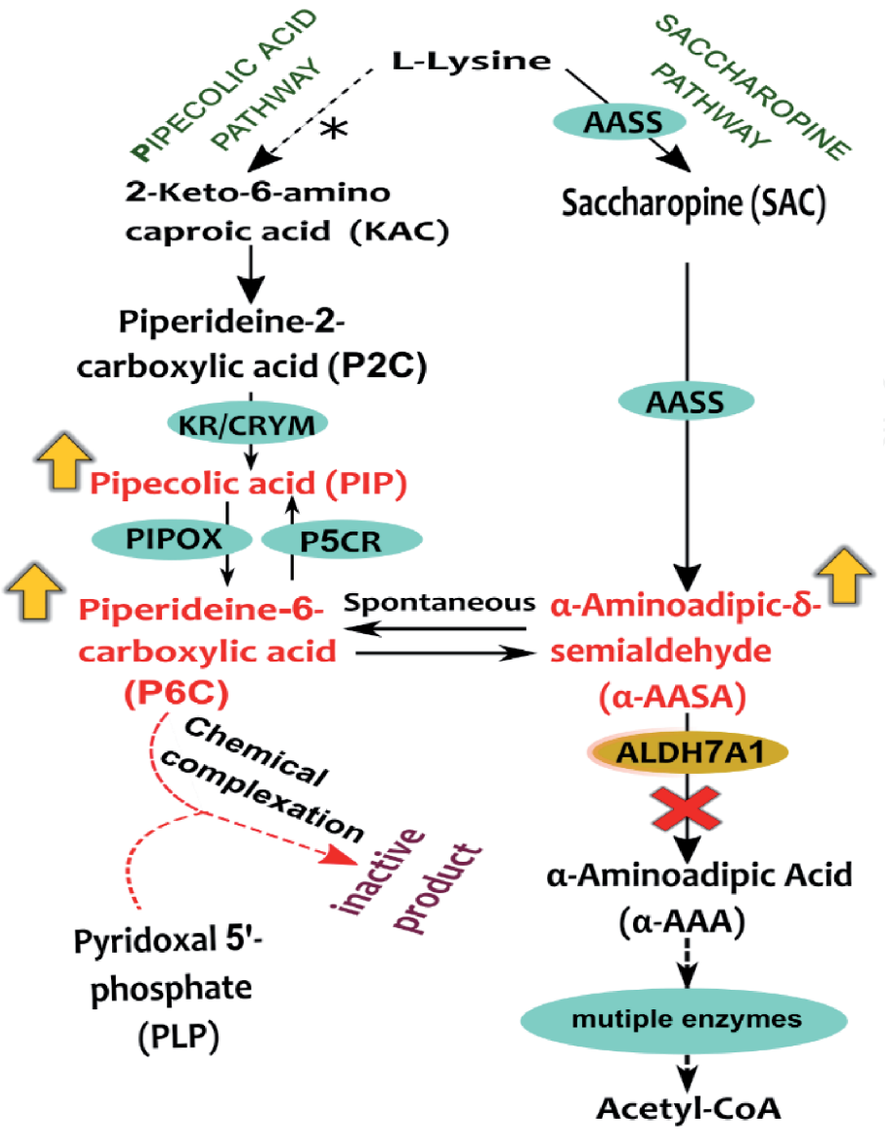


Figure 6.
*Pipecolic acid (left) and saccharopine (right) pathways for L-lysine catabolism in mammals. The two pathways converge at the step of α-AASA/P6C synthesis. ALDH7A1 catalyzes the step indicated by the red "X". Inactivation of the enzyme in PDE-ALDH7A1 causes buildup of its two substrates, P6C and α-AASA, as well as of PIP (the 3 biomarkers in patients). Accumulating P6C condenses with PLP, forming an inactive product and leading to depletion of the cofactor. *The nature of the first step of pipecolic acid pathway is undetermined. AASS: aminoadipic semialdehyde synthase; LKR: lysine-ketoglutarate reductase; SDH: saccharopine dehydrogenase; AADAT: 2-aminoadipate aminotransferase; KR: ketimine reductase; CRYM: Mu-crystallin homolog; PIPOX: pipecolic acid oxidase; P5CR: piperideine-5-carboxilic reductase. (Based on [69, 70]).*

deficiency and have been utilized as diagnostic biomarkers [72]. Recently, two additional lysine metabolites discovered to accumulate in patients have been suggested as novel biomarkers. The first one is 6-oxopipecolate (6-oxo-PIP), which was found to be present in large concentrations in plasma, urine, and CSF of ATQ deficiency patients [83, 84]. By means of an untargeted metabolomics approach, Engelke et al. [83] identified another novel metabolite, 6-(2-oxopropyl)piperidine-2-carboxylic acid (2-OPP), that accumulated in biofluids of affected individuals.

Because P6C inactivates PLP and causes cellular depletion of this enzymatic cofactor, a number of biochemical abnormalities occur that are associated with secondary deficiencies of PLP-dependent enzymes, mainly affecting amino acid metabolism. **Table 2** lists some amino acid changes reported in PDE-ALDH7A1 patients and possible links to PLP-dependent enzymes in their metabolic pathways.

Amino acid (tissue/fluid, change)*	Implicated PLP-dependent enzyme(s)**	Enzyme's function**
Glycine (CSF & plasma, ↑)	Glycine dehydrogenase (decarboxylating)	Important component of the glycine cleavage system
Threonine (CSF, ↑)	Glycine C-acetyltransferase	Catalyzes the second step in the pathway that converts threonine to glycine
	Threonine deaminase	Catalyzes the first step in the catabolic pathway of threonine [85]
Serine (plasma, ↑)	• Serine dehydratase • Serine hydroxymethyltransferase [86]	Involved in breakdown/ conversion of serine to other metabolites
Alanine (CSF & plasma, ↑)	• Alanine-glyoxylate aminotransferase • Alanine transaminase	Involved in breakdown/ conversion of alanine to other metabolites
Phenylalanine (CSF, ↑)	Aromatic L-amino acid decarboxylase	Converts phenylalanine to phenethylamine
Arginine (CSF, ↓)	Ornithine δ-aminotransferase	Catalyzes the formation of ornithine, an indirect precursor for arginine synthesis [57, 87]
Histidine (CSF, ↑)	Histidine decarboxylase	Converts histidine to histamine

**Amino acid changes were retrieved from the case series of Mills et al. [75] and Yuzyuk et al. [85].*
↑: elevated, ↓: lowered.
***Unless another source is specified, information on PLP-dependent enzymes and their catalytic activities were collectively retrieved from the review of Wilson et al. [6] and KEGG pathway database [88].*

Table 2.
Amino acid changes in PDE-ALDH7A1 and related PLP-dependent enzymes.

2.1.4 Treatment and its outcome

In patients with PDE-ALDH7A1, seizures are effectively controlled by PN treatment in about 90% of cases [6]. Patients require life-long intake of pharmacological doses of PN for seizure control as PN withdrawal leads to seizure recurrence [60]. In a subset of patients with ATQ deficiency, better seizure control is achieved when folinic acid is added to the PN regimen (known as folinic acid-responsive seizures or FARS) [60]. The subset of FARS patients can be distinguished by the appearance of a characteristic peak (Peak X) on CSF biogenic amine neurotransmitter analysis [60, 89].

Despite effective control of seizures with PN, treatment outcome is usually still poor, and a large proportion of children with PDE-ALDH7A1 have neurodevelopmental impairments [77]. It has been suggested that PN treatment alone cannot prevent the accumulation of high levels of lysine metabolites (P6C, α-AASA and PIP) in the brain which may have neurotoxic effects [90].

To limit the accumulation of these metabolites, substrate (lysine) reduction therapies have been implemented. These consisted of lysine-restricted diet [91], arginine supplementation [92] and triple therapy [93]. Arginine is a natural antagonist of lysine because the two amino acids use the same transporter (known as the y + system) for their transportation across the BBB. Therefore, it was suggested that arginine could compete with lysine and limit its entry to the brain [72, 92]. Triple

therapy refers to a combination therapy of lysine-restriction and arginine supplementation (in addition to PN treatment, therefore it was termed "triple therapy") [93]. Clinical trials using these dietary therapies reported reduction in lysine metabolite levels and improvements in the neurodevelopmental outcome in most treated patients [79, 85, 91, 93–96].

2.2 PLP-dependent epilepsy (PNPO deficiency)

2.2.1 Disease mechanism

PNPO catalyzes the rate-limiting step in the biosynthetic pathway of PLP from other vitB6 vitamers (salvage pathway, **Figure 2**). Patients affected with pathogenic variants in its encoding gene, *PNPO*, have reduced activity of PNPO which leads to dysfunction of the salvage pathway and inability of the patients to produce adequate amounts of PLP [86].

2.2.2 Clinical features

Similar to PDE-ALDH7A1, PNPO deficiency is characterized by early onset, drug-resistant epileptic encephalopathy [87]. Since the disease gene discovery in 2005 [57], about 90 cases of PNPO deficiency have been reported in the medical literature with a phenotypic spectrum that extends from early postnatal lethality to milder forms with well-controlled seizures and normal neurodevelopmental outcome [88, 97–99]. Prematurity is observed in about 50% of the PNPO deficiency cases [88]. Seizures usually start very early after birth (within the first day of life in about 60% of the cases), but can also have a later onset within the first 6 months of life [86, 88]. *In utero* onset of seizures have been suspected in some of the documented cases [87]. PNPO-deficient patients may also suffer from variable degrees of morphological brain defects, most commonly diffuse brain atrophy, and neurodevelopmental deficits [88] as well as systemic co-morbidities such as lactic acidosis, hypoglycaemia, coagulopathy, anemia and ocular and cardiac problems [6, 37, 86, 98].

2.2.3 Biochemical features and diagnostic biomarkers

PNPO deficiency is associated with a number of biochemical alterations most commonly affecting biogenic amine neurotransmitters. The PLP-dependent enzyme, AADC, plays a central role in the biosynthetic pathway of these neurotransmitters (**Figure 5**). A number of amine neurotransmitter metabolites in this pathway were found to be present at abnormal levels in PNPO-deficient patients, suggesting an impaired flux through the AADC catalyzed step. For example, elevated levels of 3-*O*-methyldopa (3-OMD) and vanillactic acid (VLA) have been frequently detected in patients' CSF and urine samples, respectively [6, 88]. Both compounds are metabolites of L-dopa, the direct precursor of dopamine, which are generated upstream of AADC [44] (**Figure 5**). On the other hand, low CSF concentrations have been detected for metabolites downstream to AADC, namely, homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) [88, 100], the catabolic products of dopamine and serotonin, respectively (**Figure 5**) [44].

The biochemical spectrum of PNPO deficiency also includes amino acid and vitB6 vitamer perturbations. Elevated concentrations of threonine, glycine, histidine and taurine and low concentrations of arginine in CSF and/or plasma

have been all reported in patients [6, 10, 88]. Unlike PDE-ALDH7A1, systemic PLP deficiency is a typical finding in PNPO deficiency as evidenced by the detection of low PLP levels in pre-treatment patient samples (CSF and/or plasma) [37, 88, 101]. Another common vitamer finding is the accumulation of PM, the precursor of PNPO substrate, detected in both pre- and post-treatment plasma samples [101, 102].

Currently there is no specific diagnostic biomarker for PNPO deficiency and genetic testing of the *PNPO* gene is required to establish diagnosis [86]. Altered biogenic amine profile along with low PLP and/or elevated PM in patient biofluids have been proposed as indicators of PNPO deficiency [6, 10, 88]. In a small cohort of patients, Mathis et al. [101] noted a consistently elevated plasma PM/PA ratio irrespective of vitB6 treatment status. This distinct vitamer profile was only observed in PNPO-deficient patients but not in other vitB6EE forms and was therefore suggested to be a candidate biomarker for PNPO deficiency, but this is yet to be validated in a larger cohort of patients [101]. Recently, a new and rapid mass spectrometry-based method has been developed for diagnosis of PNPO deficiency in dried blood spots which relies on measurement of enzyme activity [103].

2.2.4 Treatment and its outcome

Seizures are usually controlled by supplementation of pharmacological doses of PLP or PN. Based on early reports [57, 104, 105], PNPO deficiency has for some time been viewed as a disease that is only treatable by PLP but not PN (and hence was given the name "PLP-dependent epilepsy"). This was also consistent with the notion that the defective enzyme, PNPO, in these patients is unable to convert supplemented PN to PLP which explains the lack of response to PN treatment. However, it was later found that a subset of affected children (about 40% of cases [6]) show better clinical response to PN while PLP may in fact exacerbate their seizures [87, 106]. Mills et al. [87] suggested that certain genotypes (namely R225H/C and D33V) seem to be more likely to benefit from PN treatment. This was attributed to possible residual enzyme activity that is associated with these *PNPO* mutations and that PN may also have a chaperone-like stabilizing effect on the mutant protein. PLP, on the other hand, may exert an inhibitory effect on the protein and abolish its presumed residual activity leading to more deleterious consequences [106, 107]. Based on treatment response, PNPO-deficient patients appear to fall into at least 3 groups; patients who respond to PLP but are refractory to PN, patients who respond to both vitamers (PLP and PN) and patients who respond to PN but decline upon switching to PLP [86].

In some patients, better seizure control was achieved by adjunct treatments like anti-seizure drugs [106] and/or riboflavin [108] in combination with vitB6 therapy. Riboflavin is a precursor of flavin mononucleotide (FMN), the cofactor of PNPO, and therefore may enhance residual enzyme activity [87]. There were multiple reports of liver problems in patients receiving PLP treatment, and these were linked to possible toxic effects of chronic PLP administration, an observation that warrants careful mentoring of PLP-treated patients [109–111].

Neurodevelopmental outcome is still poor in a large proportion of affected children. A recent literature survey of 87 cases of PNPO deficiency [88] found that 56% of patients suffered developmental and/or intellectual deficits in spite of adequate seizure control with vitB6 therapy. Other reports suggested that early diagnosis and initiation of treatment could lead to normal developmental outcome [4, 109, 112].

2.3 Hyperprolinemia type 2

2.3.1 Disease mechanism

The genetic cause of hyperprolinemia type 2 (HP2), first identified in an Irish traveler family [64], was found to be due to recessive mutations in *ALDH4A1.* The gene codes for pyrroline 5-carboxylate dehydrogenase (P5CD), an enzyme that catalyzes an intermediate step in the proline degradation pathway [6] (**Figure 7**). In a pathobiochemical mechanism similar to PDE-ALDH7A1, deficiency of P5CD leads to accumulation of pyrroline 5-carboxylate (P5C), an intermediate metabolite that undergo a spontaneous Knoevenagel type of reaction with PLP leading to reduced bioavailability of the cofactor (**Figure 7**) [63].

2.3.2 Clinical features

The clinical manifestation of HP2 is variable [114] and asymptomatic cases have been described [115]. Seizures are the most common clinical fining in HP2 which occur in about 50% of the cases [6, 114]. They are often triggered by febrile illness and have variable age of onset; commonly occurring during infancy or childhood but can also be up to late adulthood (63 years in one HP2 case [116]) [6, 114, 117, 118]. Intellectual and neuropsychiatric abnormalities have also been described in some HP2 patients. In the original HP2 Irish traveler family, 9 out of the 13 affected individuals developed seizures and two of them had intellectual disability [118]. Van de Ven [119] reported 5 HP2 patients; all presented with seizures, 3 had intellectual disability and 4 suffered behavioral problems.

2.3.3 Biochemical features and diagnostic biomarkers

The key biochemical features of HP2 are elevated plasma and urinary levels of proline (about 10–15 folds higher in plasma) and P5C. A combination of both biomarkers is diagnostic of HP2 and distinguishes it from hyperprolinemia type 1 [119, 120]. Walker and Mills [121] identified a new metabolite,

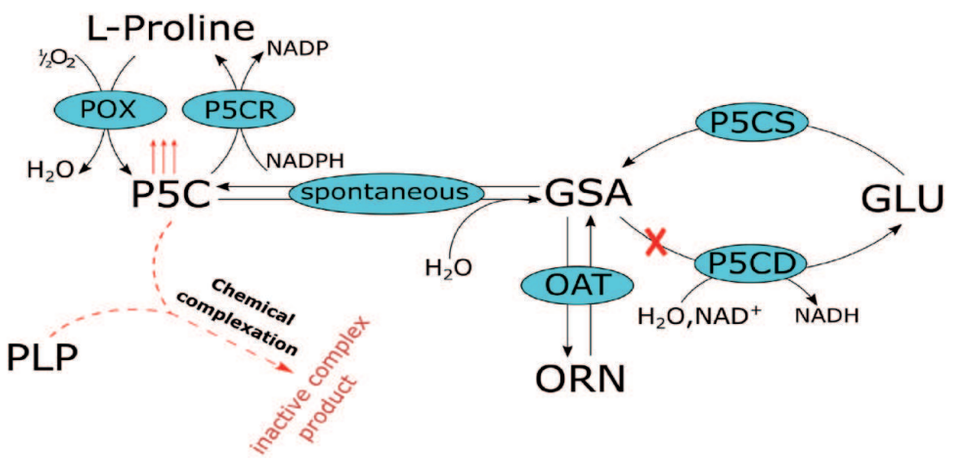


Figure 7.
L-Proline metabolic pathway. In HP2, inactivation of P5CD causes accumulation of the upstream metabolite P5C (red arrows). P5C spontaneously condenses with the enzymatic cofactor PLP leading to the formation of inactive adducts and depletion of the cofactor. GSA: glutamic-gamma-semialdehyde, ORN: ornithine, NAD(P): nicotinamide adenine dinucleotide (phosphate), POX: proline oxidase, P5CR: P5C reductase, P5C: pyrroline 5-carboxylate, OAT: ornithine aminotransferase, P5CD: P5C dehydrogenase, P5CS: P5C synthase. (Based on [63, 113]).

N-(pyrrole-2-carboxyl) glycine, that accumulated in urine of HP2 subject. They subsequently confirmed the presence of this compound in another 4 patients and suggested its use as a diagnostic biomarker for HP2. Other metabolic alterations reported in HP2 patients include increased plasma concentrations of lactate [116, 119], glycine [115, 120], ornithine [120], and alanine [119] and urinary xanthurenic acid; probably secondary to PLP deficiency [59]. VitB6 was previously analyzed in 5 HP2 patients [59, 116, 119] and found to be decreased in 3 patients and at low normal levels in the other two.

2.3.4 Treatment and its outcome

VitB6 supplementation has been used to treat HP2 associated seizures with variable response. Most of the case studies reported effective control of seizures with vitB6, either alone or in conjugation with anti-seizure medications [59, 114, 116], while few described irresponsiveness to vitB6 therapy [119]. Van de Ven et al. [119] assessed the long-term clinical outcome in 4 HP2 patients treated with vitB6 and/or anti-seizure medications. Seizures resolved spontaneously in 3 patients by the age of 12–18 years, however, neurobehavioral problems were persistent in most patients despite therapy. The clinical course was non-progressive and did not correlate with the vitB6 dose and vitB6 therapy [119].

2.4 Hypophosphatasia

2.4.1 Disease mechanism

Hypophosphatasia (HPP) results from autosomal recessive or dominant mutations affecting *ALPL*, the gene encoding tissue nonspecific alkaline phosphatase (TNSALP). TNSALP is an ecto-enzyme that is highly expressed in bone, liver, kidney and developing teeth [122, 123]. The enzyme catalyzes extracellular dephosphorylation of multiple substrates including inorganic pyrophosphate (PPi), phosphoethanolamine (PEA), and PLP (**Figure 3**) [122, 124]. On the osteoblast membrane, TNSALP hydrolyzes PPi into inorganic phosphate (Pi). Together with calcium ions (Ca^{2+}), Pi is required for the synthesis of hydroxyapatite (HA) which is the major inorganic constituent of bones and teeth. In HPP, TNSALP deficiency leads to extracellular accumulation of PPi which impairs the formation of HA and proper bone mineralization leading to an array of skeletal abnormalities [122, 123]. TNSALP is also required for the extracellular hydrolysis of PLP to PL to facilitate its entry into the cell which explains the occurrence of intracellular PLP deficiency and vitB6-dependent seizures in some forms of HPP [123, 124].

2.4.2 Clinical features

There is a remarkable heterogeneity in the clinical presentation of HPP and 5 principal clinical types have been recognized based on skeletal disease features and age of onset. In order of escalating severity, these types are “odonto”, “adult”, “childhood”, “infantile”, and “perinatal” HPP [124, 125]. The severe forms (infantile and perinatal) show autosomal recessive inheritance, while in the milder forms both autosomal dominant or recessive inheritance has been described [124, 126]. Defective mentalization of bone and/or teeth is the clinical hallmark feature of HPP in all of these types [127]. Seizures are the most well described extra-skeletal feature of HPP and are exclusively observed in the infantile and perinatal types [128]. According to a recent metanalysis [128], seizures occurred in about 20% of patients with pediatric-onset HPP.

Odonto-HPP is the mildest form and can manifest at any age. It involves minor dental problems like premature shedding of deciduous teeth without any other symptoms [123, 124]. Adult HPP typically manifest during middle age or later and can cause debilitating symptoms like osteomalacia leading to bone fractures, chondrocalcinosis, musculoskeletal pain and loss of dentition. Some patients also suffer from pseudogout due to increased extracellular concentrations of PPi [123, 126]. Childhood HPP presents after the age of 6 months and common features include rickets and premature loss of deciduous teeth. Severe forms are also associated with muscle weakness causing delay in walking and abnormal gait [125]. Infantile HPP is a severe type and can lead to death in about 50% of affected infants [123]. It is diagnosed before 6 months of age and features delayed postnatal development, failure to thrive, hypotonia along with rachitic deformities [125]. Hypercalcemia and hypercalciuria are frequently seen and may lead to renal failure [126]. In rapidly progressive cases, rickets causes thoracic deformity and death may ensue due to respiratory insufficiency [125, 129]. VitB6-dependent seizures may develop, sometimes preceding the skeletal features, and usually predict a fatal outcome [123, 125]. Perinatal HPP is the most severe type in which the symptoms start *in utero* or at birth and almost always lead to lethal outcome. Skeletal hypomineralization is profound and causes deformities such as caput membranaceum, wide fontanels and short limb dwarfism [123, 125, 130]. Chest malformation followed by pulmonary compromise is also a common fatal consequence of the rachitic disease [126]. Additional features described in this extreme form of HPP comprise vitB6-dependent seizures, apnea, irritability, myelophthisic anemia and intracranial hemorrhage [123].

2.4.3 Biochemical features and diagnostic biomarkers

HPP can be diagnosed by the presence of pathognomonic skeletal radiographic changes along with characteristic biochemical features. The most commonly used biochemical marker for HPP is low serum alkaline phosphatase activity which consistently observed in all forms of HPP [126]. Other reported biochemical findings in HPP include increased levels of TNSALP substrates PPi and PEA in urine, elevated Pi in plasma, hypercalciuria and/or hypercalcemia and high urinary levels of phosphoserine [6, 123, 124, 126]. These features can only be used to support the diagnosis of HPP because they may not be present in all HPP forms and are sometimes observed in other skeletal diseases. A more sensitive and specific biomarker for HPP is elevated serum levels of PLP, which has been detected even in the mildest form of HPP (odonto-HPP) and the degree of PLP elevation seems to correlate with disease severity [123, 131].

2.4.4 Treatment and its outcome

HPP-related seizures are usually responsive to PN supplementation [56, 129]. Effective treatment against the skeletal manifestations was lacking until the advent of Asfotase alfa, an enzyme-replacement therapy that was approved in 2015 [124, 126]. Asfotase alfa is recombinant, fusion protein consisting of the catalytic ectodomain of human TNSALP, the Fc fragment of human immunoglobulin G1 (IgG1) and a deca-aspartate motif for bone targeting [123, 131, 132]. Clinical trials have demonstrated the long-term safety and efficacy of Asfotase alfa in preventing life-threatening complications of HPP [123, 132, 133]. HPP patients, including those with severe forms, treated with Asfotase alfa showed marked improvements in all clinical aspects (radiography, pulmonary, neurodevelopmental and motor functions) along with resolution of pain and disability

[123, 126, 133]. At the biochemical level, Asfotase alfa therapy was associated with normalization of plasma levels of PPi and PLP [133].

2.5 PLPHP deficiency

2.5.1 Disease mechanism

PLPHP deficiency is the latest addition to B6EEs that is caused by recessive mutations in *PLPBP*, a gene previosly known as proline synthetase co-transcribed homolog (*PROSC*) [7]. The product of this gene, known as PLP homeostasis protein (PLPHP), belongs to a highly conserved family of proteins known to bind PLP. The function of these PLP-binding proteins in humans as well as other species is poorly understood. Their structures have remarkable similarity with a bacterial enzyme known as alanine racemase [134]. An insight into the function of this protein came from ananlysis of samples from PLPHP-deficient pateints which showed a widely deranged vitB6 vitamer profile. It has therefore been suggeseted that this protein plays an imprtant role in vitB6 homeostasis [7, 68]. However, the exact mechanism of how PLPHP dysfunction disrupts PLP homeostasis and leads to the observed epileptic encephalopathy is still unknown. Darin et al. [7] hypothesized that PLPHP is a PLP-carrier that protects the reactive cofactor from binding to other cellular molecules, shields it from degradative enzymes like phosphatases and securely delivers it to PLP-dependent enzymes.

2.5.2 Clinical features

The general clinical picture of PLPHP deficiency remarkably overlaps with that of ALDH7A1 deficiency and PNPO deficiency which is dominated by pharmaco-resistant seizures that respond to vitB6 treatment. Seizures typically manifest during the first week of life [7, 67, 68, 135] with possible prenatal onset in some cases [68] and a recent report of late onset at 14 months of age [136]. Johnstone et al. [68] reported two patients who presented with fatal mitochondrial encephalopathy and a patient with unique movement disorder who lacked epileptic seizures. Developmental delay, intellectual disability, acquired microcephaly and structural brain abnormalities are common co-morbidities observed in this form of B6EEs [7, 67, 68, 137–139]. Systemic features like metabolic acidosis, anemia and gastrointestinal problems have been also described in PLPHP-deficient pateints [7, 67].

2.5.3 Biochemical features and diagnostic biomarkers

Biochemical investigations performed in patient samples revealed amino acid and neurotransmitter abnormalities, reflecting the pleiotropic metabolic effects associated with altered PLP homeostasis. Among amino acids, elevated glycine in plasma and/or CSF was the most frequent alteration identified [7, 67, 68]. The enzyme that breaks down glycine, glycine cleavage system, requires PLP as a cofactor [140]. Abnormal monoamine neurotransmitter profile was detected in some patients, possibly due to suboptimal activity of the PLP-dependent enzyme AADC. Reported changes included low CSF levels of HVA (marker of low dopamine) and raised concentrations of 3-OMD, L-dopa, 5-HTP (CSF) and VLA (urine) indicating accumulation of AADC substrates [7, 67, 86]. Low PLP levels were detected in pre-treatment plasma [68] and CSF [7] samples from two patients. Johnstone et al. [68] described accumulation of high levels of PNP in patient fibroblasts and PLPHP-deficient HEK293 cells. There is currently no established biomarker for this disease.

2.5.4 Treatment and its outcome

Seizures typically respond well to vitB6 treatment (PN in majority of cases). In cases with inadequate response to PN, switching to PLP led to better seizure control [67]. About half of the cases required additional anti-seizure medications for optimal seizure control [7, 67]. The addition of folinic acid resulted in improved seizure control in one patient [68].

While seizures and secondary metabolic alterations are usually normalized with vitB6 therapy, a major fraction of patients still develop some form of neurodevelopmental disability. A recent review of 45 published PLPHP deficiency cases found that 65% of the patients suffered from intellectual disability [67]. The underlying pathophysiological mechanism is not well understood, and currently there is no effective treatment against the neurodevelopmental phenotype of this disorder.

3. Other vitB6-responsive conditions

The therapeutic effect of vitB6 supplementation have been also described in other disease conditions. The following section outlines some examples.

3.1 Hyperphosphatasia with mental retardation syndrome

Hyperphosphatasia with mental retardation (HPMR) syndrome (OMIM Phenotypic Series: PS239300) refers to a group of congenital disorders caused by defects in the biosynthetic pathway of glycosyl phosphatidylinositol (GPI) anchor. GPI-anchor is a glycolipid that is required for tethering of TNSALP and several other proteins (more than 150 in total) to the cell surface and at the blood–brain barrier (BBB) [6, 61]. Six subtypes of HPMR syndrome have been identified to date with variable phenotypic spectrum that extends from mild nonsyndromic intellectual disability (ID) to more complex forms with severe ID, seizures, increased serum alkaline phosphates and dysmorphic features [141–143]. Low serum PLP has been detected in some patients which may be ascribed to the elevated serum level of alkaline phosphate [144]. Seizures in some HPMR subtypes like PIGV deficiency [144] and PIGO deficiency [143] have been shown to respond to pyridoxine treatment.

3.2 PL kinase deficiency

PL kinase (PLK) is an important enzyme in the vitB6 salvage pathway (**Figure 2**). It is responsible for phosphorylating different vitameric compounds which is a pre-requisite step for their subsequent conversion to the active cofactor PLP (**Figure 2**). Biallelic mutations in the gene encoding PLK (*PDXK*) have been recently shown to cause an autosomal recessive disorder that is characterized by axonal peripheral polyneuropathy and optic atrophy [145]. Affected subjects had low plasma PLP and treatment with PLP supplementation was associated with biochemical and clinical improvements [145].

3.3 Molybdenum cofactor deficiency

Molybdenum cofactor (MoCoF) deficiency is a severe inherited metabolic disease that causes intractable seizures, developmental delay and structural brain

defects. It is due to recessive mutations in either *MOCS1*, *MOCS2* or *GPHN*, all of which are important genes in the MoCoF biosynthetic pathway [146]. MoCoF deficiency impairs the activity of three MoCoF-dependent enzymes; sulfite oxidase, xanthine dehydrogenase and aldehyde oxidase [146, 147]. Patients with MoCoF deficiency excrete elevated levels of a number of metabolites, most notably sulfite and α-AASA [147] (the latter is the same metabolite that accumulates in PDE-ADLH7A1). *In vitro* experiments [147] demonstrated that sulfite inhibits the activity of ADLH7A1 which explains the accumulation of α-AASA in MoCoF deficiency. It is postulated that increased α-AASA, and consequently its cyclic form P6C, may lead to nonenzymatic trapping of PLP [148], in a mechanism analogous to that seen in PDE-ADLH7A1 (**Figure 6**). In line with this, Footitt et al. [149] described low CSF PLP levels in two MoCoF deficiency patients. Struys et al. [148] reported pyridoxine-responsive seizures in two patients with MoCoF deficiency due to *MOCS2* mutations.

3.4 Defects in PLP-dependent enzymes

In addition to its coenzymatic role, binding of PLP to its apo-enzymes may also be required for proper folding and correct subcellular targeting of these enzymes [6, 150]. Several inborn errors affecting PLP-dependent enzymes have been described to benefit from PN therapy. Examples are homocystinuria (cystathionine β-synthase deficiency), X-linked sideroblastic anemia (δ-aminolevulinate synthase deficiency), primary hyperoxaluria type I (alanine: glyoxylate aminotransferase (AGT) deficiency), ornithine aminotransferase deficiency and AADC deficiency [6, 9, 150]. The therapeutic effect of PN supplementation could to be attributed to the chaperone-like, stabilizing action of PLP on these mutated proteins [150]. In primary hyperoxaluria type I, it has been hypothesized that at high concentration, PLP promotes AGT dimerization and inhibit the accumulation of monomeric protein species which are mistargeted to the mitochondria [6, 150]. A recent addition to this category of PN-responsive disorders came from the discovery of *GOT2* mutations in patients who presented with a novel form of epileptic encephalopathy and serine deficiency [151]. *GOT2* encodes the PLP-dependent enzyme glutamate oxaloacetate transaminase (mitochondrial isoform). PN supplementation, either alone or in combination with serine, led to seizure control in these patients [151].

3.5 Other epileptic disorders

High-dose vitB6 treatment has been used for seizure control in several other epileptic disorders not related to vitB6 metabolism or its dependent enzymes; such as channelopathies [152–154] and West syndrome [155–157]. The specific mechanism of vitB6-repsosivness in these types of seizure disorders is not well recognized. Some authors [6, 154] suggested that vitB6 may have anticonvulsant effects because of the ability of PLP to block P2 purinoceptor 7 (P2X7 receptors), as demonstrated *in vitro* [158].

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