

Inborn errors affecting vitamin B₆ metabolism

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Vitamin B₆ is an important vitamin for normal brain function. The metabolism of dietary vitamin B₆ to its active cofactor pyridoxal 5'-phosphate is described. The mechanism of action of pyridoxal 5'-phosphate is described, as are some important functions in the brain. The clinical features and biochemistry of three inborn errors of metabolism affecting brain pyridoxal 5'-phosphate concentrations are described, each of which cause early-onset epilepsy of variable severity. These are pyridoxine phosphate oxidase deficiency, hyperprolinemia Type 2 and pyridoxine-dependent epilepsy caused by antiquitin deficiency. Hypophosphatasia is also discussed briefly, as the epilepsy that can complicate this disorder appears to be due to pyridoxal phosphate deficiency. Lastly, the antiepileptic properties of pyridoxine and pyridoxal phosphate are discussed.

Vitamin B₆ is important for normal brain function, particularly in the immature brain [1]. Vitamin B₆ deficiency causes seizures and, if untreated, can lead to permanent neurological sequelae. This review describes the transport and metabolism of vitamin B₆ and the role of alkaline phosphatases. The clinical features and pathogenesis of three inborn errors of metabolism that cause deficiency of the active cofactor pyridoxal 5'-phosphate are also discussed (Table 1).

Vitamin B₆ metabolism

Vitamin B₆ is a water-soluble vitamin that is present in the body as six vitamers: pyridoxine (pyridoxol), pyridoxamine, pyridoxal and their 5'-phosphorylated esters. Only pyridoxal phosphate has cofactor activity.

Vitamin B₆ is ingested from the diet and is present in many foods including meats, pulses, cereals, vegetables and some fruit; a proportion is also derived from intestinal bacterial flora. Animal-derived vitamin B₆ consists mostly of phosphorylated pyridoxal and pyridoxamine, whilst that from plants consists largely of free and bound pyridoxine [1]. Phosphorylated B₆ vitamers are converted to their free bases by intestinal alkaline phosphatases and these are then absorbed from the upper small intestine by a carrier-mediated system [2]. Absorption is rapid and the vitamers pass into the portal blood and are taken up by the liver. Here, pyridoxine, pyridoxamine and pyridoxal are phosphorylated by pyridoxal kinase to their 5'-phosphate esters and pyridoxine phosphate and pyridoxamine phosphate oxidized by pyridox(am)ine phosphate oxidase to form

pyridoxal phosphate. Pyridoxal phosphate is released from the liver into the circulation where it is bound by albumin and forms approximately 60% of circulating vitamin B₆ with lesser amounts of pyridoxine, pyridoxamine and pyridoxal (Figure 1).

Only the free vitamin bases can cross the blood-brain barrier, mostly at the choroid plexi (Figure 1) [3]. Pyridoxal phosphate is first cleaved to pyridoxal by nonspecific membrane-associated alkaline phosphatases and transported into cerebrospinal fluid (CSF) by an active transport mechanism that can also take-up pyridoxine and pyridoxamine. Uptake of the free vitamins from CSF into brain cells is via a similar mechanism. The importance of the membrane nonspecific alkaline phosphatases in the uptake of vitamin B₆ into the CNS is illustrated by a mouse model lacking alkaline phosphatase. These mice die from intractable epilepsy but can be rescued by treatment with pyridoxal or a dietary source of vitamin B₆ [4]. In humans with hypophosphatasia – an inherited disorder of bone mineralization caused by decreased function of tissue nonspecific alkaline phosphatase – we, and others [5], have noted that complicating seizures also respond to pyridoxine. Once in the brain cell, vitamin B₆ is trapped by phosphorylation of pyridoxal, pyridoxine and pyridoxamine catalyzed by pyridoxine kinase [6]. Pyridoxine and pyridoxamine phosphate are then oxidized by pyridox(am)ine 5'-phosphate oxidase to form pyridoxal phosphate [7]. Pyridoxal phosphate exhibits feedback inhibition upon pyridox(am)ine 5'-phosphate oxidase [8], but the regulation of brain pyridoxal phosphate concentrations is likely to be complex [7].

Keywords: α -aminoaldehyde, antiquitin, encephalopathy, epilepsy, hyperprolinemia Type 2, hypophosphatasia, pipercolic acid, pyridoxal phosphate, pyridoxine, pyridoxine-dependent epilepsy, pyridoxine phosphate oxidase, vitamin B₆

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Table 1. Inborn errors of metabolism causing deficiency of brain pyridoxal 5'-phosphate.

Inborn error of metabolism	Mechanism	Consequence
Hypophosphatasia	Decreased absorption or transport	Seizures
Pyridox(am)ine phosphate oxidase deficiency	Decreased biosynthesis	Epileptic encephalopathy
Hyperprolinemia Type II	Consumption	Seizures
Pyridoxine-dependent epilepsy	Consumption	Epileptic encephalopathy

Actions of pyridoxal phosphate

Pyridoxal phosphate has excellent electron sink properties that make it a versatile organic catalyst. With the exception of glycogen phosphorylase, all enzymes that utilize pyridoxal phosphate as a cofactor act upon amino acids or amines. The aldehyde group of pyridoxal phosphate can undergo a Schiff base reaction with free amine groups to form an aldimine double-bond linking the amino acid to the electron sink. The unique environment produced by the enzyme protein determines the catalytic properties and the type and specificity of the holoenzyme [9]. More than 100 apoenzymes are known that require pyridoxal phosphate as a cofactor and the holoenzymes catalyze diverse reaction specificities, such as transamination, decarboxylation, racemization, elimination and replacement reactions.

In the brain, pyridoxal phosphate-dependent enzymes are involved in the metabolism of many amino acid and amine neurotransmitters, such as dopamine, serotonin, glutamate, glycine, γ -aminobutyric acid (GABA), D-serine and taurine (Table 2). These enzymes are also important in the synthesis of neuroprotective compounds, such as kynurenic acid. Thus, defects in the metabolism of pyridoxal phosphate would be expected to have major neurological consequences. It has long been known that vitamin B₆ deficiency in human infants is a cause of epilepsy [10].

Inborn errors of vitamin B₆ metabolism

Four disorders are thought to be caused by defective vitamin B₆ metabolism or transport. Hypophosphatasia is mentioned above under vitamin B₆ metabolism. Pyridox(am)ine 5'-phosphate oxidase deficiency causes a pyridoxine non-responsive, pyridoxal phosphate responsive neonatal epileptic encephalopathy [11]. Type II hyperprolinemia can cause pyridoxine responsive epilepsy [12]. This is caused by inactivation of pyridoxal phosphate by the accumulating pyrroline-5-carboxylic acid resulting in pyridoxal

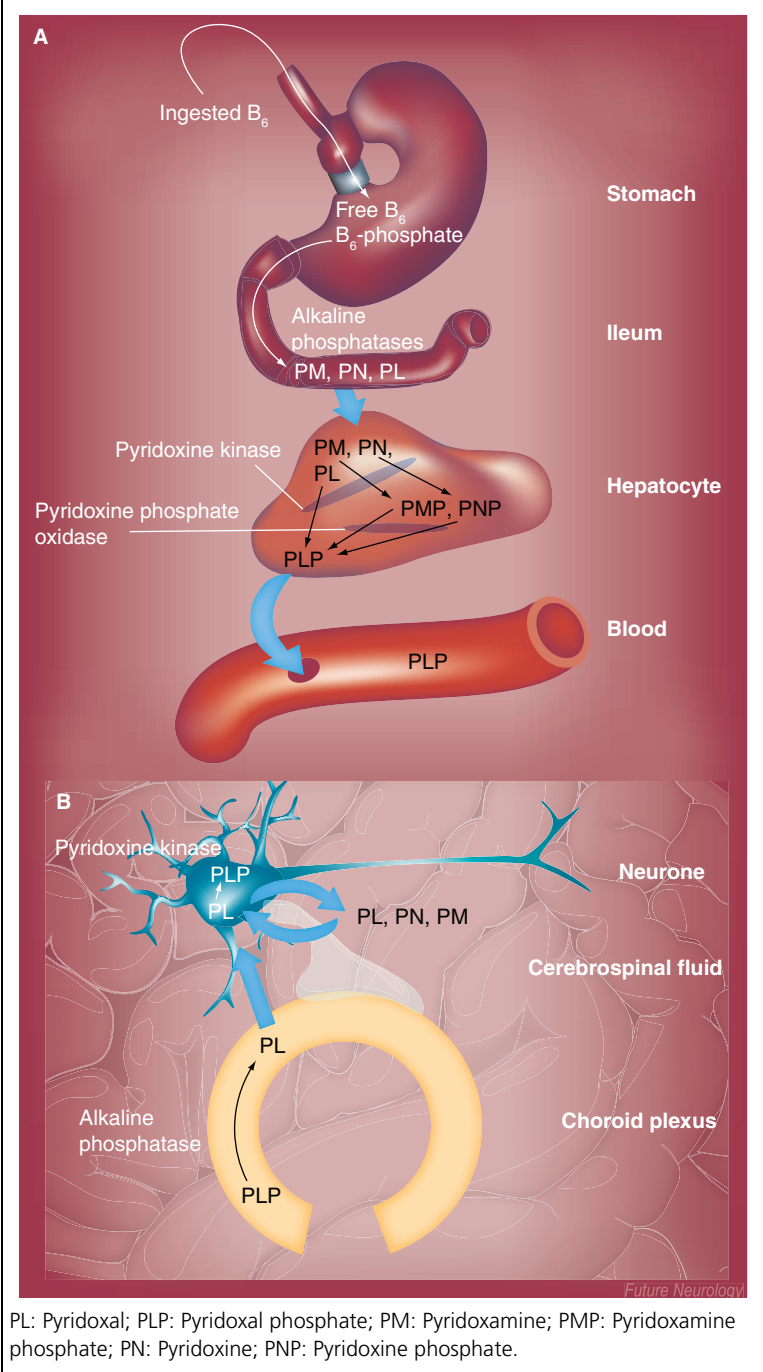
phosphate deficiency [13]. Pyridoxine-dependent epilepsy has long been thought of as an inborn error of vitamin B₆ metabolism or transport [14], but recently a major cause has been found to be a deficiency of α -amino adipic semialdehyde dehydrogenase, which also causes inactivation of pyridoxal phosphate [15].

Pyridox(am)ine 5'-phosphate oxidase deficiency

Only five patients are currently known to have pyridox(am)ine phosphate oxidase deficiency [11], and a further probable case had pyridoxine non-responsive, pyridoxal phosphate-responsive epilepsy [16]. The infants were born prematurely with evidence of fetal distress. All had impaired postnatal adaptation resembling hypoxic-ischemic neonatal encephalopathy with a persistent lactic acidosis. Seizures developed in the first 12 h of life and were resistant to conventional antiepileptic therapy. Multiple seizure types developed and electroencephalography evolved to a burst-suppression pattern. There is no (or a very incomplete) response to intravenous pyridoxine, but one patient responded promptly to pyridoxal phosphate at a dose of 10 mg/kg administered every 6 h [17]. This response was associated with an initial severe cerebral depression (as seen in a proportion of cases with pyridoxine-dependent epilepsy, described below).

All patients had characteristic biochemical findings in CSF, plasma and urine that were due to a block in metabolic pathways caused by deficiency of a pyridoxal phosphate-dependent enzyme. There were reduced homovanillic and 5-hydroxyindolacetic acid concentrations and raised 3-methoxytyrosine (aromatic L-amino acid decarboxylase deficiency), glycine (glycine cleavage enzyme) and threonine (threonine dehydratase) concentrations in the CSF. Similar, but more variable, changes were found in plasma. Urine showed increased excretion of vanillactic acid (aromatic L-amino acid decarboxylase deficiency).

Figure 1. The absorption, transport and metabolism of vitamin B₆.



hyperprolinemia developed seizures and an encephalopathic illness in association with pneumonia and was found to be pyridoxal phosphate-deficient [12]. The seizures responded well to pyridoxine 50 mg orally per day. It was subsequently shown that pyrroline-5-carboxylate condenses with, and deactivates, pyridoxal phosphate [13]. At the time this was a novel mechanism of vitamin antagonism.

Pyridoxine-dependent epilepsy

The phenomenon of pyridoxine-dependent epilepsy has been known since 1954 [20]; however, it appears to be rare, with a birth incidence of around one in every 400,000 [21]. Pyridoxine-dependent epilepsy is classified into an early-onset, typical group presenting within the first few days of life, and into a late-onset, atypical group presenting thereafter until up to 3 years of age [22]. In the early-onset presentation there may be prenatal seizures from approximately 20 weeks of gestation. There is often (in approximately a third) neonatal encephalopathy with hyperalertness, irritability and a stimuli-sensitive startle, this can be accompanied by systemic features such as respiratory distress, abdominal distension and vomiting, and a metabolic acidosis. Multiple seizure types, especially generalized tonic, clonic or myoclonic, start within the first few days and are resistant to conventional anti-epileptic medication. The electroencephalogram (EEG) is abnormal with diffuse slow-wave activity, which may be discontinuous, with intermingled spike and polyspike foci; in many, a severe EEG abnormality with a 'burst suppression' pattern is observed [23]. However, most patients will be receiving antiepileptic drug therapy before the EEG is performed, which makes interpretation difficult [24]. There may be structural brain abnormalities, such as hypoplasia of the posterior part of the corpus callosum, cerebellar hypoplasia or hydrocephalus and other cerebral complications such as hemorrhage or white matter abnormalities [25]. There is a prompt (within minutes) response to pyridoxine 100 mg administered intravenously with cessation of all seizure activity. However, in approximately 20% of infants with pyridoxine-dependent epilepsy the first dose of pyridoxine can also cause cerebral depression. The infants usually become hypotonic and sleep for some hours, it can rarely involve apnea, cardiovascular instability and an isoelectric EEG. Cerebral depression with the first dose of pyridoxine is more likely if the infant is receiving anticonvulsant drugs.

Type II hyperprolinemia

Type II hyperprolinemia is caused by a deficiency of Δ^1 -pyrroline-5-carboxylate dehydrogenase. This causes the accumulation of proline and pyrroline-5-carboxylate in plasma and excessive excretion of pyrroline-5-carboxylate in urine [18]. In childhood, Type II hyperprolinemia causes generalized seizures in approximately half of the affected individuals [19]. One child with Type II

Table 2. Some of the pyridoxal 5'-phosphate-dependent enzymes important in brain neurotransmitter metabolism.

Enzyme	Function
Aromatic amino acid decarboxylase	Dopamine and serotonin synthesis
Branched chain amino acid, 2-oxoglutarate aminotransferase	Glutamate synthesis
GABA transaminase	GABA catabolism
Glutamate decarboxylase	GABA synthesis
Glycine cleavage enzyme	Glycine catabolism
Kynureninase	Quinolinic acid synthesis
Kynurenine aminotransferase	Kynurenic acid synthesis
L-serine racemase	D-serine synthesis

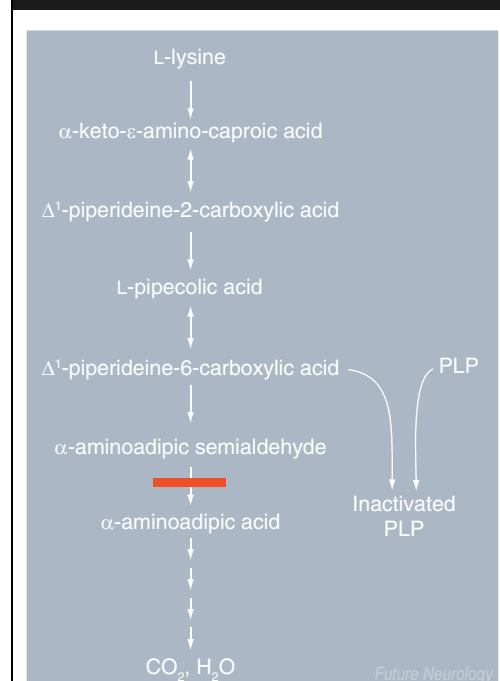
GABA: γ -amino butyric acid.

By contrast, late-onset pyridoxine-dependent epilepsy has no encephalopathy and no brain structural abnormalities. Seizures may commence at any time up to 3 years of age [26]. Often, these are seizures occurring in the context of a febrile illness, which may develop into status epilepticus. There is usually an initial response to conventional anti-epileptic drugs but it becomes increasingly difficult to control the seizures with time. Pyridoxine in a dose of 100 mg/day orally causes the cessation of seizure activity within 1–2 days. Cerebral depression is not a complication of administration of pyridoxine in late-onset pyridoxine-dependent epilepsy.

Until recently (see below), the only way to confirm a diagnosis of pyridoxine-dependent epilepsy was to withdraw pyridoxine and demonstrate the recurrence of seizures that again demonstrate a prompt response to pyridoxine. Treatment is life-long and the usual dose of pyridoxine is approximately 15 mg/kg/day up to 500 mg/kg/day. Learning difficulties, particularly language, seem to be a common complication of early-onset pyridoxine-dependent epilepsy [25]. Delay in treatment over months or years causes a severe motor disorder with learning difficulties and sensory impairment. Every neonate with seizures, even if the suspected diagnosis is perinatal asphyxia or sepsis, should therefore be given a trial of intravenous pyridoxine. Similarly, every child with the onset of epilepsy under 3 years of age should also have a trial of oral pyridoxine [27].

The most common cause of pyridoxine-dependent epilepsy has recently been elucidated [15]. Mutations of the *aldehyde dehydrogenase (ALDH) 7A1* gene, which encodes antiquitin, abolish the activity of antiquitin as an α -aminoadipic semialdehyde dehydrogenase, resulting in the accumulation of L- Δ^1 -piperidine-6-carboxylate (P6C). α -aminoadipic semialdehyde dehydrogenase is part of the pipercolic pathway of lysine catabolism

(Figure 2). P6C can condense with pyridoxal phosphate and presumably inactivates it, causing brain pyridoxal phosphate deficiency [15]. The *ALDH7A1* gene has been mapped to chromosome 5q31, which is known to be the most common locus for pyridoxine-dependent epilepsy [28,29]. This finding also explains the raised pipercolic acid, known to be a biochemical marker of pyridoxine-dependent epilepsy [30], and suggests a simpler way of confirming the diagnosis by the measurement of urinary α -aminoadipic semialdehyde excretion.

Figure 2. The pipercolic acid pathway of lysine catabolism.

The red rectangle shows the site of the metabolic block in pyridoxine-dependent epilepsy. Δ^1 -piperidine-6-carboxylic acid condenses with pyridoxal phosphate to form inactivated PLP. PLP: Pyridoxal phosphate.

Pyridoxine & pyridoxal phosphate responsive seizures

In clinical practice, particularly in the Far East, pyridoxine and pyridoxal phosphate have been used as antiepileptic drugs in infantile spasms and childhood generalized and focal epilepsy [31]. In one series of infants with infantile spasms of all etiologies, over 10% with symptomatic and over 20% with idiopathic spasms responded to pyridoxal phosphate; these had a better prognosis than the group that failed to respond [32]. Subsequently, pyridoxal phosphate could be withdrawn without recurrence of seizures. Similar findings have been found with treatment of infantile spasms with pyridoxine [33], although this remains controversial [34]. In a large group of children with medically intractable idiopathic epilepsy (both partial and generalized seizures), almost 10% responded to treatment with pyridoxal phosphate [35]: of these, half also responded to pyridoxine. In childhood epilepsy, pyridoxine and pyridoxal phosphate can be considered as antiepileptic drugs [36,37]; although it is unknown what proportion of responders might have a defect in vitamin B₆ metabolism or transport.

Conclusion

Inborn errors of metabolism can affect vitamin B₆ metabolism by reducing synthesis of the active cofactor pyridoxal 5'-phosphate or by inactivating it. Each known inborn error causes epilepsy of varying severity; all appear to be rare disorders.

However, more common epilepsies can respond to pyridoxine or pyridoxal phosphate and it is unknown whether such responders might have an inborn error of vitamin B₆ metabolism or transport.

Future perspective

Despite the major advances in recent years in our understanding of defects in vitamin B₆ metabolism, there remain many interesting questions. What causes the epilepsy in the pyridoxal phosphate-deficient brain? Is it dysfunction of one (or more) of the pyridoxal-phosphate dependent enzymes? If so, are there inborn errors affecting this enzyme that also cause epilepsy? If not, does pyridoxal phosphate have a noncofactor role? Can it interact with ion channels or with ionic pumps? Are pyridoxine and pyridoxal phosphate antiepileptic drugs? All known cases of pyridox(am)ine phosphate oxidase deficiency have had mutations with less than 30% residual activity, but do milder deficiencies exist and cause later-onset epilepsy? What might be the other cause(s) of pyridoxine-dependent epilepsy? What neurological syndromes might be caused by vitamin B₆ transporter deficiency? Can other vitamins be inactivated in the same way as pyridoxal phosphate?

To try and answer such questions will require the careful study of vitamin B₆ metabolism in children with epilepsy. The methods to do this exist and we are sure that in the near future answers to many of the questions will become known.

Executive summary

Vitamin B₆ metabolism

- Dietary vitamin B₆ consists mostly of pyridoxine (PN) and its glucoside (from vegetables) and pyridoxal phosphate and pyridoxamine (PM) (from meat).
- Free vitamins PN, PM and pyridoxal (PL) are absorbed and then phosphorylated in the liver by pyridoxine kinase (PK).
- Pyridoxine phosphate and pyridoxamine phosphate are then oxidized to pyridoxal phosphate (PLP) by pyridox(am)ine 5'-phosphate oxidase (PNPO).
- PLP appears to be the major transport form of vitamin B₆, and is also the active cofactor form.
- The mechanisms of uptake into the CNS are not entirely clear, but a facilitated carrier mechanism for PL, PN and PM exists (but not their 5'-phosphorylated derivatives).
- PLP has been identified as the cofactor for approximately 100 enzymes involved in amine and amino acid metabolism. These include many enzymes important in the metabolism of neurotransmitters and other neurotoxic and neuroprotective compounds.

Inborn errors affecting vitamin B₆ metabolism

- Of the possible inborn errors of vitamin B₆ metabolism and transport, only one is known (PNPO deficiency). Two inborn errors of other pathways (pyridoxine-dependent epilepsy and hyperprolinemia type II) cause PLP deficiency in the brain by a chemical interaction.
- The clinical features of PNPO deficiency and pyridoxine-dependent epilepsy are those of early-onset epileptic encephalopathies, responding to PLP and PN, respectively.
- Approximately half of all children with hyperprolinemia Type II develop early-onset epilepsy that responds to PN.
- Hypophosphatasia is an inherited disorder of bone mineralization caused by the reduced function of tissue nonspecific alkaline phosphatase. This is occasionally complicated by seizures that respond to PN.

Pyridoxine & pyridoxal phosphate-responsive epilepsy

- In some circumstances it seems that pyridoxine and pyridoxal phosphate can be effective antiepileptic drugs. However, the proportion of patients with such pyridoxine responsive epilepsy who might have a defect in vitamin B₆ metabolism or transport is unknown.

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