Vitamin B-6[1]

Vitamin B-6 is a water-soluble vitamin first discovered as a factor that cured dermatitis in rats. There are 6 forms of vitamin B-6 found in mammals. The naturally occurring forms of the vitamin include pyridoxine (PN), pyridoxal (PL), pyridoxamine (PM), and their respective monophosphorylated derivatives (PNP, PLP, and PMP). PN, PL, and PM are converted to pyridoxal 5′-phosphate (PLP) through the consecutive actions of *1*) a kinase that phosphorylates the 5′hydroxymethyl group and *2*) pyridoxamine phosphate oxidase (PNPO), which acts on PNP and PMP. PLP is the biologically active form of the vitamin that functions as an enzyme cofactor and/or regulator for >140 enzyme-catalyzed reactions. PLP-dependent proteins account for ~4% of total cellular enzymes. PLP is covalently bound to the active sites of aminotransferases, decarboxylases, racemases, and dehydratases, among other enzymes, through a Schiff's base between the aldehyde of PLP and the ε-amino of an active site lysine. PLP-dependent enzymes play essential roles in amino acid metabolism, glycolysis, gluconeogenesis, glycogenolysis, transsulfuration, polyamine biosynthesis, and synthesis of sphingoid bases (required for myelin formation) and the heme precursor δ-aminolevulinic acid. In energy metabolism, PLP-dependent transaminases allow interconversion of amino acids and intermediates in energy-generating pathways. In the brain, PLP is required for the synthesis of the neurotransmitters serotonin, norepinephrine, epinephrine, and γ-aminobutyrate (GABA), and as such is involved in both neuronal excitation and inhibition. Vitamin B-6 is catabolized through the oxidation of pyridoxal to 4-pyridoxic acid, which is excreted in urine.

Deficiencies

The NHANES 2003–2006 estimated a prevalence of 10.6% for vitamin B-6 deficiency with the use of serum cutoff values for PLP <20 nmol/L (1). Suboptimal or marginal vitamin B-6 status is typically defined as plasma PLP concentrations in the range of 20–30 nmol/L. Vitamin B-6 status has been shown to be inversely correlated with cardiovascular disease, stroke, diabetes, and cancer. Clinical symptoms of PLP deficiency include depression, nervousness, impaired immune response, and irritability. In children and adults, severe vitamin B-6 deficiency can be a cause of sideroblastic microcytic anemia due to depressed hemoglobin synthesis, seizures that are refractory to conventional medications, convulsions, and peripheral neuropathy. Pyridoxine intake at 8 μg/(kg · day) reverses irritability and seizures in vitamin B-6–deficient infants.

PNPO deficiency, an inborn error of metabolism that impairs the conversion of PN to PLP, causes PLP deficiency, low PLP concentrations in cerebrospinal fluid, and neonatal epileptic encephalopathy. Other risk factors for low vitamin B-6 status that are independent of dietary vitamin B-6 intake include low-dose oral contraceptive use, alcoholism, preeclampsia, and inflammation, but it is not clear how these factors affect plasma vitamin B-6 concentrations and if they create frank deficiency. Low vitamin B-6 status does not cause inflammation.

Diet Recommendations

The RDA for vitamin B-6 was last reviewed in 1998 (**Table 1**). Plasma PLP concentration remains the most commonly used measure of vitamin B-6 status, reflects liver concentrations, and is mostly refractory to fluctuation in daily vitamin B-6 intake. The RDA is estimated from the level of vitamin B-6 intake required to achieve a plasma PLP concentration of at least 20 nmol/L. For infants aged 0–6 mo, an Adequate Intake (AI) was estimated on the basis of the vitamin B-6 content of human milk from well-nourished mothers and normal human-milk intake by infants. For infants aged 7–12 mo, the AI was based on extrapolations from the Estimated Average Requirement (EAR) for adults and from the AI for infants aged 0–6 mo. The concentration of vitamin B-6 in milk depends on the mother's vitamin B-6 intake, and therefore the EAR for lactating women is estimated to ensure the human-milk vitamin B-6 concentrations of 130 μg/L are achieved.

Food Sources

The primary dietary forms of vitamin B-6 from natural sources are PLP and PNP. Rich sources of total vitamin B-6 include fortified ready-to-eat cereals; fish; liver and other organ meats; potatoes and other starchy vegetables; legumes; nuts, bananas, avocados, and other noncitrus fruits; egg yolks; whole grains; and vegetables. Plant-based vitamin B-6 sources contain high amounts of glycosylated PN [pyridoxine-5′-β-D-glucoside (PNG)], which has lower bioavailability than PN but is converted to PN by cytosolic PNG hydrolase (PNGH) and brush border lactase-phlorizin hydrolase. Fortified breads and cereals may also contain vitamin B-6 as PN. The activity of nonspecific intestinal phosphatases is required for gut absorption, and the nonphosphorylated forms of the vitamin are transported across the blood-brain barrier. Bioavailability of vitamin B-6 is estimated to be 75% from a varied diet.

Clinical Uses

Inborn errors of metabolism resulting from recessive mutations in genes encoding PLP-dependent enzymes can benefit from PN therapy, including X-linked sideroblastic anemia, xanthurenic aciduria, primary hyperoxaluria type 1, cystathionuria, homocystinuria, gyrate atrophy, aromatic L-amino acid decarboxylase deficiency, and pyridoxine-dependent epilepsy resulting from α-aminoadipic-semialdehyde dehydrogenase

 Adv. Nutr. 6: 132–133, 2015; doi:10.3945/an.113.005207.

TABLE 1 Dietary Reference Intakes for vitamin B-6[1]

Age group	Vitamin B-6 RDA, mg/d	UL, mg PN/d
Infants		
0–6 mo	0.1 (AI)	—
7–12 mo	0.3 (AI)	—
Children		
1–3 y	0.5	30
4–8 y	0.6	40
9–13 y	1.0	60
Adolescents: 14–18 y		
Boys	1.3	80
Girls	1.2	80
Adults		
19–50 y (men and women)	1.3	100
>51 y		
Men	1.7	100
Women	1.5	100
Pregnancy	1.9	80 (14–18 y) 100 (>19 y)
Lactation	2.0	80 (14–18 y) 100 (>19 y)

[1]AI, Adequate Intake; PN, pyridoxine; UL, Tolerable Upper Intake Level.

mutations. Early infant supplementation with PLP results in clinical improvement in cases of PNPO deficiency.

Supplemental vitamin B-6 has been shown to be beneficial for therapeutic treatment of certain adult-onset clinical conditions. The combination of supplemental L-methylfolate, methylcobalamin, and PLP increases epidermal nerve fiber density in the lower extremity of patients with diabetic peripheral neuropathy and reduces the associated paresthesias and/or dysesthesias. PN therapy may be beneficial for kidney transplant recipients with primary hyperoxaluria type 1. In 2014, the FDA approved the use of doxylamine-pyridoxine therapy for the treatment of nausea and vomiting during pregnancy.

Toxicity

There are no known adverse outcomes resulting from high intakes of vitamin B-6 from natural food sources. The Tolerable Upper Intake Level for vitamin B-6 is based on adverse effects caused by high doses of supplemental PN (**Table 1**). PN can be neurotoxic, causing sensory ataxic neuropathy that is not reversible in many cases. Dermatologic lesions have also been reported with excess PN intake.

Recent Research

Gold-standard biomarkers of PLP function are lacking. PLP-dependent pathways differ in their sensitivity to changes in vitamin B-6 status, and many serum vitamin B-6 functional biomarkers change in response to ≥1 additional nutrient deficiencies or physiologic states. Current approaches to identifying metabolic/functional biomarkers of vitamin B-6 status involve simultaneous assessment of a panel of metabolites involved in the PLP-dependent pathways of tryptophan catabolism, one-carbon metabolism, and transsulfuration including creatine, cystathionine, kynurenic acid, and 3-hydroxykynurenine.

Patrick J Stover*
Martha S Field
Division of Nutritional Sciences, Cornell University, Ithaca, NY

[1]Author disclosures: PJ Stover and MS Field, no conflicts of interest.

*To whom correspondence should be addressed. E-mail: pjs13@cornell.edu.

Reference

1. U.S. Centers for Disease Control and Prevention. Second National Report on Biochemical Indicators of Diet and Nutrition in the U.S. Population 2012. Atlanta (GA): National Center for Environmental Health; April 2012.

For further information:

National Research Council. Dietary Reference Intakes: the essential guide to nutrient requirements. Washington, DC: The National Academies Press; 2006.

Cellini B, Montioli R, Oppici E, Astegno A, Voltattorni CB. The chaperone role of the pyridoxal 5′-phosphate and its implications for rare diseases involving B6-dependent enzymes. Clin Biochem 2014;47:158–65.

Slaughter SR, Hearns-Stokes R, van der Vlugt T, Joffe HV. FDA approval of doxylamine-pyridoxine therapy for use in pregnancy. N Engl J Med 2014;370:1081–3.