Cholecalciferol

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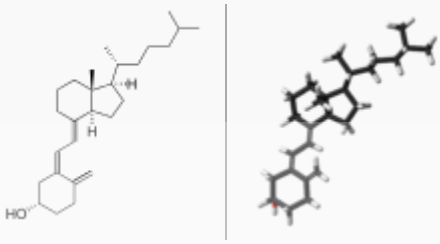

IUPAC name

(3β,5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-trien-3-ol

Other names

vitamin D_3, activated 7-dehydrocholesterol.

Identifiers

CAS number	67-97-0
PubChem	5280795
ChemSpider	4444353
UNII	1C6V77QF41
EC number	200-673-2
DrugBank	DB00169
ChEBI	CHEBI:28940
ChEMBL	CHEMBL1042
ATC code	A11CC05
Jmol-3D images	Image 1

SMILES

O[C@@H]1CC(\C(=C)CC1)=C\C=C2/CCC[C@]3([C@H]2CC[C@@H]3[C@H](C)CCCC(C)C)C

InChI

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Key: QYSXJUFSXHHAJI-YRZJJWOYSA-N

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Properties	
Molecular formula	$C_{27}H_{44}O$
Molar mass	384.64 g/mol
Appearance	White, needle-like crystals
Melting point	83–86 °C
Boiling point	496.4 °C
Except where noted otherwise, data are given for materials in their standard state (at 25 °C (77 °F), 100 kPa)	

Cholecalciferol (also known as toxiferol[*citation needed*]) is a form of vitamin D, also called **vitamin D_3.**[1][2]

It is structurally similar to steroids such as testosterone, cholesterol, and cortisol (though vitamin D_3 itself is a secosteroid).

Forms

Vitamin D_3 has several forms:

- Cholecalciferol (sometimes called calciol) is an inactive, unhydroxylated form of vitamin D_3).
- Calcifediol (also called calcidiol, hydroxycholecalciferol, 25-hydroxyvitamin D_3, etc. and abbreviated 25(OH)D) is one of the forms measured in the blood to assess vitamin D status.[3]
- Calcitriol (also called 1,25-dihydroxyvitamin D_3) is the active form of D_3[4]

Metabolism

7-Dehydrocholesterol is the precursor of vitamin D_3. Within the epidermal layer of skin,[5] 7-Dehydrocholesterol undergoes an electrocyclic reaction as a result of UVB radiation, resulting in the opening of the vitamin precursor B-ring through a conrotatory pathway. Following this, the

previtamin D_3 undergoes a [1,7] antarafacialsigmatropic rearrangement [6] and therein finally isomerizes to form vitamin D_3.

Cholecalciferol is then hydroxylated in the liver to become calcifediol (25-hydroxyvitamin D_3).

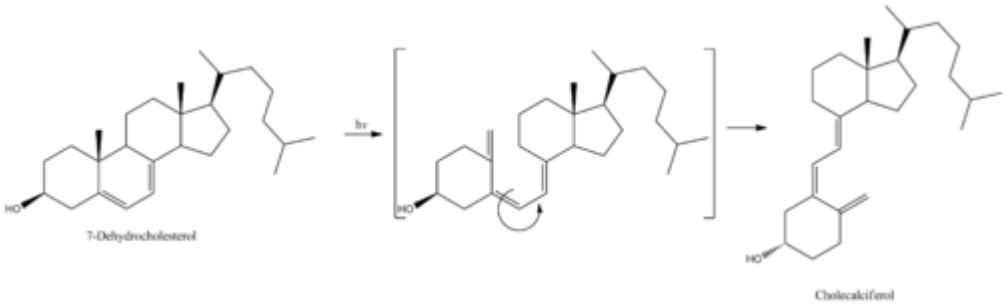
Next, calcifediol is again hydroxylated, this time in the kidney, and becomes calcitriol (1,25-dihydroxyvitamin D_3). Calcitriol is the most active hormone form of vitamin D_3.

Regulation of metabolism

- Cholecalciferol is synthesized in the skin from 7-dehydrocholesterol under the action of ultraviolet B light. It reaches an equilibrium after several minutes depending on several factors including conditions of sunlight (latitude, season, cloud cover, altitude), age of skin, and color of skin.
- Hydroxylation in the endoplasmic reticulum of liver hepatocytes of cholecalciferol to calcifediol (25-hydroxycholecalciferol) by 25-hydroxylase is loosely regulated, if at all, and blood levels of this molecule largely reflect the amount of vitamin D_3 produced in the skin or the vitamin D_2 or D_3 ingested.
- Hydroxylation in the kidneys of calcifediol to calcitriol by 1-alpha-hydroxylase is tightly regulated (stimulated by either parathyroid hormone or hypophosphatemia) and serves as the major control point in production of the most active circulating hormone calcitriol (1,25-dihydroxyvitamin D_3).

Industrial production

Cholecalciferol is produced industrially for use in vitamin supplements and to fortify foods by the ultraviolet irradiation of 7-dehydrocholesterol extracted from lanolin found in sheep's wool. Paraphrasing a more detailed explanation,[7] cholesterol is extracted from wool grease and wool wax alcohols obtained from the cleaning of wool after shearing. The cholesterol undergoes a four step process to make 7-dehydrocholesterol, the same compound that is stored in the skin of animals. The 7-dehydrocholesterol is then irradiated with ultra violet light. Some unwanted isomers are formed during irradiation. These are removed by various techniques, leaving a resin which melts at about room temperature and usually has a potency of 25,000,000 to 30,000,000 International Units per gram.



Cholecalciferol is also produced industrially for use in vitamin supplements from lichens, which is suitable for vegans.[8][9]

An alternative compound is ergocalciferol (also known as vitamin D_2) derived from the fungal sterol ergosterol.

Dose

One gram is 40,000,000 ($40x10^6$) IU, equivalently 1 IU is 0.025 µg.

Recommendations vary depending on the country. In the US they are: 15 µg/d (600 IU per day) for all individuals (males, female, pregnant/lactating women) under the age of 70 years-old. For all individuals older than 70 years, 20 µg/d (800 IU per day) is recommended.[10] (Recommendations in Europe: 5 µg/d, in France: 25 µg) A growing body of researchers question whether the current recommended adequate levels are sufficient to meet physiological needs, particularly for individuals deprived of regular sun exposure or those at higher risk such as those with higher melanin content in the skin (i.e., those whose ancestors are

African, Middle Eastern, Latin American, Mediterranean or Asian), the obese, and those who live far from the equator. The upper limit (UL) for vitamin D has been recommended as 4,000 IU daily. The 4,000-IU cut-off was determined by the Institute of Medicine in 2010 after reviewing the then-current medical literature, finding that the dose for lowest observed adverse effect level is 40,000 IU daily for at least 12 weeks,[11] and that there was a single case of toxicity above 10,000 IU after more than 7 years of daily intake; this case of toxicity occurred in circumstances that have led other researchers to dispute it as a credible case to consider when making vitamin D intake recommendations.[11] The Institute of Medicine did not find evidence of toxicity between 4,000 IU and 10,000 IU, so the 4,000-IU figure is more of an estimate than a number based on evidence of toxicity above 4,000 IU.[10] Patients with severe vitamin D deficiency will require treatment with a loading dose; its magnitude can be calculated based on the actual serum 25-hydroxy-vitamin D level and body weight.[12]

Also, there is a therapy for rickets utilizing a single dose, called *stoss* therapy in Europe, taking from 300,000 IU (7,500 µg) to 500,000 IU (12,500 µg = 1.25 mg), in a single dose, or in two to four divided doses.[13]

The 25-hydroxy vitamin D (calcifediol) blood test is used to determine how much vitamin D is in the body. The normal range of calcifediol is 30.0 to 74.0 ng/ml.[3]

"Vitamin D2 toxicity can result from regular excess intake of this vitamin, and may lead to hypercalcemia and excess bone loss. Individuals at particular risk include those with hyperparathyroidism, kidney disease, sarcoidosis, tuberculosis, or histoplasmosis. Chronic hypercalcemia may lead to serious or even life-threatening complications, and should be managed by a physician. Early symptoms of hypercalcemia may include nausea, vomiting, and anorexia (appetite/weight loss), followed by polyuria (excess urination), polydipsia (excess thirst), weakness, fatigue, somnolence, headache, dry mouth, metallic taste, vertigo, tinnitus (ear ringing), and ataxia (unsteadiness). Kidney function may become impaired, and metastatic calcifications (calcium deposition in organs throughout the body) may occur, particularly affecting the kidneys. Treatment involves stopping the intake of vitamin D or calcium, and lowering the calcium levels under strict medical supervision, with frequent monitoring of calcium levels. Acidification of urine and corticosteroids may be necessary."[14]

There are conflicting reports concerning the absorption of cholecalciferol (D_3) versus ergocalciferol (D_2), with some studies suggesting less efficacy of D_2,[15] and others showing no difference.[16] At present, D_2 and D_3 doses are frequently considered interchangeable, but more research is needed to clarify this.

Stability

Cholecalciferol is very sensitive to UV radiation and will rapidly, but reversibly, break down to form sura-sterols, which can further irreversibly convert to ergosterol

Preventative application

A 2008 study published in Cancer Research has shown the addition of vitamin D_3 (along with calcium) to the diet of some mice fed a regimen similar in nutritional content to a new Western diet with 1000 IU cholecaliferol per day prevented colon cancer development.[17] In humans, with 400 IU daily, there was no effect;[18] however, significant correlation exists between low levels of blood serum cholecalciferol and higher rates of various cancers, multiple sclerosis,tuberculosis, heart disease, and diabetes.[19]

Objecting the conclusions of the results of recent randomized clinical trials (RCTs), which used "low dose, lack of compliance, cross-over, and poor follow-up" and had concluded that Vitamin D supplementation is unnecessary for most people, Dr. Ed Gorham from the UCSD Department of Family and Preventive Medicine: "Many epidemiologic advances have been based on observational studies. It is fortunate we didn't rely on RCTs to recognize the hazards of cigarette smoking or second-hand smoke, which were determined through case-control studies and cohort studies respectively. To his undying credit, Dr. John Snow did not resort to forcing some residents of Broadstreet to drink from that pump supplying water contaminated by cholera. Do

our ethics allow us to withhold vitamin D to only 800 IU in a placebo group such as that of VITAL? 800 IU would on average raise baseline serum vitamin D levels barely 8 ng/ml. VITAL will place half the participants at risk of what is finally becoming regarded by vitamin D experts as the vitamin D deficiency syndrome. Likewise, the meager 2,000 IU per day given to the treatment group in Vital will still fall short of many of the benefits of vitamin D sufficiency which become apparent when patients achieve a 40-60ng/ml 25(OH)D range."

Toxicity

Rodents are somewhat more susceptible to high doses than other species, and cholecalciferol has been used in poison bait for the control of these pests. It has been claimed that the compound is less toxic to non-target species. However, in practice it has been found that use of cholecalciferol in rodenticides represents a significant hazard to other animals, such as dogs and cats. "Cholecalciferol produces hypercalcemia, which results in systemic calcification of soft tissue, leading to renal failure, cardiac abnormalities, hypertension, CNS depression, and GI upset. Signs generally develop within 18-36 hr of ingestion and can include depression, anorexia, polyuria, and polydipsia."[20]

In New Zealand, possums have become a significant pest animal, and cholecalciferol has been used as the active ingredient in lethal gel baits and cereal pellet baits "DECAL" for possum control. The LD_{50} is 16.8 mg/kg, but only 9.8 mg/kg if calcium carbonate is added to the bait.[21][22]

Kidneys and heart are target organs.[23]

See also

- Hypervitaminosis D, Vitamin D poisoning
- Ergocalciferol, vitamin D_2.
- 25-Hydroxyvitamin D3 1-alpha-Hydroxylase, a kidney enzyme that converts calcifediol to calcitriol.

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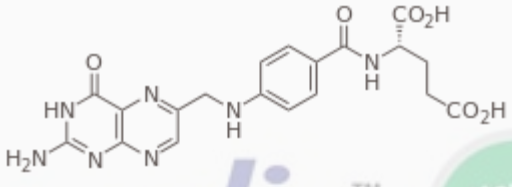
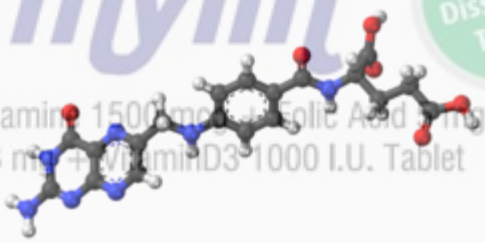
Folic acid

Folic acid





IUPAC name

(2*S*)-2-[(4-{[(2-amino-4-hydroxypteridin-6-yl)methyl]amino}phenyl)formamido]pentanedioic acid

Other names

N-(4-{[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]amino}benzoyl)-L-glutamic acid; pteroyl-L-glutamic acid; Vitamin B_9; Vitamin B_c; Folacin

Identifiers

CAS number	59-30-3
PubChem	6037
ChemSpider	5815
UNII	935E97BOY8

DrugBank	DB00158
KEGG	C00504
ChEBI	CHEBI:27470
ChEMBL	CHEMBL1622
RTECS number	LP5425000
ATC code	B03BB01
Jmol-3D images	Image 1

SMILES

O=C(N[C@H](C(O)=O)CCC(O)=O)C1=CC=C(NCC2=NC(C(NC(N)=N3)=O)=C3N=C2)C=C1

InChI

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Key: OVBPIULPVIDEAO-LBPRGKRZBH

Properties

Molecular formula	$C_{19}H_{19}N_7O_6$
Molar mass	441.40 g mol^{-1}
Appearance	yellow-orange crystalline powder
Melting point	250 °C (523 K) (decomposition) [1]
Solubility in water	1.6 mg/L (25 °C)[1]
log P	-2.5
Acidity (pK_a)	1st: 4.65, 2nd: 6.75, 3rd: 9.00[2]

Hazards

NFPA 704	 0 1 0
Except where noted otherwise, data are given for materials in their standard state (at 25 °C (77 °F), 100 kPa)	

Folic acid (also known as **vitamin M**, **vitamin B_9**,[3] **vitamin B_c**[4] (or **folacin**), **pteroyl-L-glutamic acid**, and **pteroyl-L-glutamate**)[*dubious – discuss*] is a form of thewater-soluble vitamin B_9.[5] **Folate** is a naturally occurring form of the vitamin, found in food, while folic acid is synthetically produced, and used in fortified foods andsupplements.[6] Folic acid is itself not biologically active, but its biological importance is due to tetrahydrofolate and other derivatives after its conversion to dihydrofolic acid in the liver.[7]

Vitamin B_9 (folate converted from folic acid) is essential for numerous bodily functions. Humans cannot synthesize folate *de novo*; therefore, folate has to be supplied through the diet to meet their daily requirements. The human body needs folate to synthesize DNA, repair DNA, and methylate DNA as well as to act as a cofactor in certain biological reactions.[8] It is especially important in aiding rapid cell division and growth, such as in infancy and pregnancy. Children and adults both require folate to producehealthy red blood cells and prevent anemia.[9]

Folate and folic acid derive their names from the Latin word *folium*, which means "leaf". Folate occurs naturally in many foods and, among plants, are especially plentiful in dark green leafy vegetables.[10]

A lack of dietary folates can lead to folate deficiency. A complete lack of dietary folate takes months before deficiency develops as normal individuals have about 500–20,000 µg[11] of folate in body stores.[12] This deficiency can result in many health problems, the most notable one being neural tube defects in developing embryos. Common symptoms of folate deficiency include diarrhea, macrocytic anemia with weakness or shortness of breath, nerve damage with weakness and limb numbness (peripheral neuropathy),[13] pregnancy complications, mental confusion, forgetfulness or other cognitive deficits, mental depression, sore or swollen tongue, peptic or mouth ulcers, headaches, heart palpitations, irritability, and behavioral disorders. Low levels of folate can also lead to homocysteine accumulation.[8] DNA synthesis and repair are impaired, which could lead to cancer development.[8]

Health benefits and risks

Pregnancy

Adequate folate intake during the preconception period (which is the time right before and just after a woman becomes pregnant) helps protect against a number ofcongenital malformations, including neural tube defects (which are the most notable birth defects that occur from folate deficiency).[14] Neural tube defects are severe abnormalities of the central nervous system that develop in babies during the first few weeks of pregnancy resulting in malformations of the spine, skull, and brain; the most common neural tube defects are spina bifida and anencephaly. The risk of neural tube defects is significantly reduced when supplemental folic acid is consumed in addition to a healthy diet before conception and during the first month after conception.[15][16] Supplementation with folic acid has also been shown to reduce the risk of congenital heart defects, cleft lips,[17] limb defects, and urinary tract anomalies.[18] Folate

deficiency during pregnancy may also increase the risk of preterm delivery, infant low birth weight and fetal growth retardation, as well as increasing homocysteine level in the blood, which may lead to spontaneous abortion and pregnancy complications, such asplacental abruption and pre-eclampsia.[19] Women who could become pregnant are advised to eat foods fortified with folic acid or take supplements in addition to eating folate-rich foods to reduce the risk of serious birth defects.[20] Taking 400 micrograms of synthetic folic acid daily from fortified foods and/or supplements has been suggested for all non-pregnant women, in order to have adequate folic acid intake even in case of unplanned pregnancies.[21] The RDA for folate equivalents for pregnant women is set at 600 micrograms,[22] although a range of 400 micrograms up to 4 milligrams (4000 micrograms) reported in an old U.S. Public Health Service guideline is still followed by many health care providers.[21][23][24][25] The mechanisms and reasons why folic acid prevents birth defects is unknown.[26] It is hypothesized that the insulin-like growth factor 2 gene is differentially methylated and these changes in IGF2 result in improved intrauterine growth and development.[26] Approximately 85% of women in an urban Irish study reported using folic acid supplements before they become pregnant, but only 18% used enough folic acid supplements to meet the current folic acid requirements due, it is reported, to socio-economic challenges.[27] Folic acid supplements may also protect the fetus against disease when the mother is battling a disease or taking medications or smoking during pregnancy.[28]

It also contributes to oocyte maturation, implantation, placentation, in addition to the general effects of folic acid and pregnancy. Therefore, it is necessary to receive sufficient amounts through the diet to avoid subfertility.[29]

There is growing concern worldwide that prenatal high folic acid in the presence of low vitamin B12 causes epigenetic changes in the unborn predisposing them to metabolic syndromes, central adiposity and adult diseases such as Type 2 diabetes.[30] Another active area of research and concern is that either too much or too little folic acid in utero causes epigenetic changes to the brain leading to autism spectrum disorders.[31][32][33]

Fertility

Folate is necessary for fertility in both men and women. It contributes to spermatogenesis. Therefore, it is necessary to receive sufficient amounts through the diet to avoidsubfertility.[29] Also, polymorphisms in genes of enzymes involved in folate metabolism could be one reason for fertility complications in some women with unexplained infertility.[34]

Heart disease

Taking folic acid does not reduce cardiovascular disease even though it reduces homocysteine levels.[35]

Folic acid supplements consumed before and during pregnancy may reduce the risk of heart defects in infants.[36]

Stroke

Folic acid appears to reduce the risk of stroke, which may be due to the role folate plays in regulating homocysteine concentration. The reviews indicate the risk of stroke appears to be reduced only in some individuals, but a definite recommendation regarding supplementation beyond the current RDA has not been established for stroke prevention.[37] Observed stroke reduction is consistent with the reduction in pulse pressure produced by folate supplementation of 5 mg per day, since hypertension is a key risk factor for stroke. Folic supplements are inexpensive and relatively safe to use, which is why stroke or hyperhomocysteinemia patients are encouraged to consume daily B vitamins including folic acid.[38]

Cancer

Folic acid supplementation does not appear to affect the rate of cancer.[39][40]

Diets high in folate are associated with decreased risk of colorectal cancer; some studies show the association is stronger for folate from foods alone than for folate from foods and supplements,[41] One broad cancer screening trial reported a potential harmful effect of too much folate intake on breast cancer risk, suggesting routine folate supplementation should not be

recommended as a breast cancer preventive.[42] Most research studies associate high dietary folate intake with a reduced risk of prostate cancer.[43]

Antifolates

Folate is important for cells and tissues that rapidly divide.[44] Cancer cells divide rapidly, and drugs that interfere with folate metabolism are used to treat cancer.
The antifolate methotrexate is a drug often used to treat cancer because it inhibits the production of the active form of THF from the inactive dihydrofolate (DHF). However, methotrexate can be toxic,[45][46][47] producing side effects, such as inflammation in the digestive tract that make it difficult to eat normally. Also, bone marrow depression (inducing leukopenia and thrombocytopenia), and acute renal and hepatic failure have been reported.

Folinic acid, under the drug name leucovorin, a form of folate (formyl-THF), can help "rescue" or reverse the toxic effects of methotrexate.[48] Folinic acid is *not* the same as folic acid. Folic acid supplements have little established role in cancer chemotherapy.[49][50] There have been cases of severe adverse effects of accidental substitution of folic acid for folinic acid in patients receiving methotrexate cancer chemotherapy. It is important for anyone receiving methotrexate to follow medical advice on the use of folic or folinic acid supplements. The supplement of folinic acid in patients undergoing methotrexate treatment is to give cells dividing less rapidly enough folate to maintain normal cell functions. The amount of folate given will be depleted by rapidly dividing cells (cancer) very quickly and so will not negate the effects of methotrexate.

Psychological

Some evidence links a shortage of folate with depression.[51] Limited evidence from randomised controlled trials showed using folic acid in addition to SSRIs may have benefits.[52] Research at the University of York and Hull York Medical School has found a link between depression and low levels of folate.[53] One study by the same team involved 15,315 subjects.[54] However, the evidence is probably too limited at present for this to be a routine treatment recommendation.[*according to whom?*] Folic acid supplementation affects noradrenaline and serotonin receptors within the brain, which could be the cause of folic acid's possible ability to act as an antidepressant.[55][56] The exact mechanisms involved in the development of schizophrenia are not entirely clear, but may have something to do with DNA methylation and one carbon metabolism, and these are the precise roles of folate in the body.[57]

Macular degeneration

A substudy of the Women's Antioxidant and Folic Acid Cardiovascular Study published in 2009 reported use of a nutritional supplement containing folic acid, pyridoxine, and cyanocobalamin decreased the risk of developing age-related macular degeneration by 34.7%.[58]

Folic Acid, B_{12} and Iron

There is a complex interaction between folic acid, vitamin B_{12} and iron. A deficiency of one may be "masked" by excess of another so the three must always be in balance.[59][60][61]

Toxicity

The risk of toxicity from folic acid is low, because folate is a water-soluble vitamin and is regularly removed from the body through urine.[62] One potential issue associated with high dosages of folic acid is that it has a masking effect on the diagnosis of pernicious anaemia (vitamin B_{12} deficiency),[25] and a variety of concerns[*clarification needed*] of potential negative impacts on health.[63]

Folate deficiency

Main article: Folate deficiency

Folate deficiency may lead to glossitis, diarrhea, depression, confusion, anemia, and fetal neural tube defects and brain defects (during pregnancy).[64] Folate deficiency is accelerated by alcohol

consumption.[65] Folate deficiency is diagnosed by analyzing CBC and plasma vitamin B_{12} and folate levels.[64] CBC may indicate megaloblastic anemia but this could also be a sign of vitamin B_{12} deficiency.[64] A serum folate of 3 µg/L or lower indicates deficiency.[64] Serum folate level reflects folate status but erythrocyte folate level better reflects tissue stores after intake.[64] An erythrocyte folate level of 140 µg/L or lower indicates inadequate folate status.[64] Increased homocysteine level suggests tissue folate deficiency but homocysteine is also affected by vitamin B_{12} and vitamin B_6, renal function, and genetics.[64]

One way to differentiate between folate deficiency from vitamin B_{12} deficiency is by testing for methylmalonic acid levels.[64] Normal MMA levels indicate folate deficiency and elevated MMA levels indicate vitamin B_{12} deficiency.[64] Folate deficiency is treated with supplemental oral folate of 400 to 1000 µg per day.[64] This treatment is very successful in replenishing tissues, even if deficiency was caused by malabsorption.[64] Patients with megaloblastic anemia need to be tested for vitamin B_{12} deficiency before folate treatment, because if the patient has vitamin B_{12} deficiency, folate supplementation can remove the anemia, but can also worsen neurologic problems.[64] Morbidly obese patients with BMIs of greater than 50 are more likely to develop folate deficiency.[66] Patients with celiac disease have a higher chance of developing folate deficiency.[66] Cobalamin deficiency may lead to folate deficiency, which, in turn, increases homocysteine levels and may result in the development of cardiovascular disease or birth defects.[67]

Malaria

Some studies show iron-folic acid supplementation in children under 5 may result in increased mortality due to malaria; this has prompted the World Health Organization to alter their iron-folic acid supplementation policies for children in malaria-prone areas, such as India.[68]

Dietary reference intake

Because of the difference in bioavailability between supplemented folic acid and the different forms of folate found in food, the dietary folate equivalent (DFE) system was established. One DFE is defined as 1 µg (microgram) of dietary folate, or 0.6 µg of folic acid supplement.

National Institutes of Health (US) Nutritional Requirements[69] (µg per day)

Age	Infants (RDI)	Infants (UL)	Adults (RDI)	Adults (UL)	Pregnant women (RDI)	Pregnant women (UL)	Lactating women (RDI)	Lactating women (UL)
0–6 months	65	None set	–	–	–	–	–	–
7–12 months	80	None set	–	–	–	–	–	–
1–3 years	–	–	150	300	–	–	–	–
4–8 years	–	–	200	400	–	–	–	–
9–13 years	–	–	300	600	–	–	–	–
14–18	–	–	400	800	600	800	500	800
19+	–	–	400	1000	600	1000	500	1000

The Dietary Reference Intake (DRIs) were developed by the United States National Academy of Sciences to set reference values for planning and assessing nutrient intake for healthy people. DRIs incorporate two reference values, theReference Daily Intake (RDI, the daily intake level that is adequate for 97–98% of the population in the United States where the standards were set) and tolerable upper intake levels (UL, the highest level of intake that is known to avoid toxicity). The UL for folate refers to only synthetic folate, as no health risks have been associated with high intake of folate from food sources.[69]

Sources

Folate naturally occurs in a wide variety of foods, including vegetables (particularly dark green leafy vegetables), fruits and fruit juices, nuts, beans, peas, dairy products, poultry and meat, eggs, seafood, grains, and some beers.[10][70]Spinach, liver, yeast, asparagus, and Brussels sprouts are among the foods with the highest levels of folate.[10]

Folic acid is added to grain products in many countries, and in these countries, fortified products make up a significant source of the population's folic acid intake.[71] Because of the difference in bioavailability between supplemented folic acid and the different forms of folate found in food, the dietary folate equivalent (DFE) system was established. 1 DFE is defined as 1 µg of dietary folate, or 0.6 µg of folic acid supplement. This is reduced to 0.5 µg of folic acid if the supplement is taken on an empty stomach.[72]

Folate naturally found in food is susceptible to high heat and ultraviolet light, and is soluble in water.[73] It is heat-labile in acidic environments and may also be subject to oxidation.[73]

Some meal replacement products do not meet the folate requirements as specified by the RDAs.[74]

Folate (B9) can also be processed from the pro-vitamin Pteroylmonoglutamic acid (Vitamin B10).

History

In the 1920s, scientists believed folate deficiency and anemia were the same condition.[75] A key observation by researcher Lucy Wills in 1931 led to the identification of folate as the nutrient needed to prevent anemia during pregnancy. Dr. Wills demonstrated anemia could be reversed with brewer's yeast. Folate was identified as the corrective substance in brewer's yeast in the late 1930s, and was first isolated in and extracted from spinach leaves by Mitchell and others in 1941.[76] Bob Stokstad isolated the pure crystalline form in 1943, and was able to determine its chemical structure while working at the Lederle Laboratories of the American Cyanamid Company.[77] This historical research project, of obtaining folic acid in a pure crystalline form in 1945, was done by the team called the "folic acid boys," under the supervision and guidance of Director of Research Dr. Yellapragada Subbarow, at the Lederle Lab, Pearl River, NY.[78] This research subsequently led to the synthesis of the antifolate aminopterin, the first-ever anticancer drug, the clinical efficacy was proven by Sidney Farber in 1948. In the 1950s and 1960s, scientists began to discover the biochemical mechanisms of action for folate.[75] In 1960, experts first linked folate deficiency to neural tube defects.[75] In the late 1990s, US scientists realized, despite the availability of folate in foods and in supplements, there was still a challenge for people to meet their daily folate requirements, which is when the US implemented the folate fortification program.[75]

Biological roles

DNA and cell division

Folate is necessary for the production and maintenance of new cells, for DNA synthesis and RNA synthesis, and for preventing changes to DNA, and, thus, for preventing cancer.[44] It is especially important during periods of frequent cell division and growth, such as infancy and pregnancy. Folate is needed to carry one-carbon groups for methylation reactions and nucleic acid synthesis (the most notable one being thymine, but also purine bases).[79] Thus, folate deficiency hinders DNA synthesis and cell division, affecting

hematopoietic cells and neoplasms the most because of their greater frequency of cell division. RNA transcription, and subsequent protein synthesis, are less affected by folate deficiency, as the mRNA can be recycled and used again (as opposed to DNA synthesis, where a new genomic copy must be created). Since folate deficiency limits cell division, erythropoiesis, production of red blood cells, is hindered and leads to megaloblastic anemia, which is characterized by large immature red blood cells. This pathology results from persistently thwarted attempts at normal DNA replication, DNA repair, and cell division, and produces abnormally large red cells called megaloblasts (and hypersegmented neutrophils) with abundant cytoplasm capable of RNA and protein synthesis, but with clumping and fragmentation of nuclear chromatin. Some of these large cells, although immature (reticulocytes), are released early from the marrow in an attempt to compensate for the anemia.[80] Both adults and children need folate to make normal red and white blood cells and prevent anemia.[81] Deficiency of folate in pregnant women has been implicated in neural tube defects (NTD); therefore, many developed countries have implemented mandatory folic acid fortification in cereals, etc. NTDs occur early in pregnancy (first month), therefore women must have abundant folate upon conception. Folate is required to make red blood cells and white blood cells and folate deficiency may lead to anemia, which further leads to fatigue and weakness and inability to concentrate.[82]

Biochemistry of DNA base and amino acid production

In the form of a series of tetrahydrofolate (THF) compounds, folate derivatives are substrates in a number of single-carbon-transfer reactions, and also are involved in the synthesis of dTMP(2′-deoxythymidine-5′-phosphate) from dUMP (2′-deoxyuridine-5′-phosphate). It is a substrate for an important reaction that involves vitamin B_{12} and it is necessary for the synthesis of DNA, and so required for all dividing cells.[18]

The pathway leading to the formation of tetrahydrofolate (FH_4) begins when folic acid (F) is reduced to dihydrofolate (DHF) (FH_2), which is then reduced to THF. Dihydrofolate reductasecatalyses the last step.[83] Vitamin B_3 in the form of NADPH is a necessary cofactor for both steps of the synthesis. Thus, hydride molecules are transferred from NADPH to the C6 position of the pteridine ring to reduce folic acid to THF.[84]

Methylene-THF (CH_2FH_4) is formed from THF by the addition of a methylene bridge from one of three carbon donors: formate, serine, or glycine. Methyl tetrahydrofolate (CH_3-THF, or methyl-THF) can be made from methylene-THF by reduction of the methylene group with NADPH.

Another form of THF, 10-formyl-THF, results from oxidation of methylene-THF or is formed from formate donating formyl group to THF. Also, histidine can donate a single carbon to THF to form methenyl-THF.

Vitamin B_{12} is the only acceptor of methyl-THF, and this reaction produces methyl-B_{12} (methylcobalamin). There is also only one acceptor for methyl-B_{12}, homocysteine, in a reaction catalyzed by homocysteine methyltransferase. These reactions are of importance because a defect in homocysteine methyltransferase or a deficiency of B_{12} may lead to a so-called "methyl-trap" of THF, in which THF is converted to a reservoir of methyl-THF which thereafter has no way of being metabolized, and serves as a sink of THF that causes a subsequent deficiency in folate.[77] Thus, a deficiency in B_{12} can generate a large pool of methyl-THF that is unable to undergo reactions and will mimic folate deficiency.

The reactions that lead to the methyl-THF reservoir can be shown in chain form:

folate → dihydrofolate → tetrahydrofolate ↔ methylene-THF → methyl-THF

Conversion to biologically active derivatives

All the biological functions of folic acid are performed by tetrahydrofolate and other derivatives. Their biological availability to the body depends upon dihydrofolate reductase action in the liver. This action is unusually slow in humans, being less than 2% of that in rats. Moreover, in contrast to rats, an almost-5-fold variation in the activity of this enzyme exists between humans.[7] Due to this low activity, it has been suggested this limits the conversion of folic acid into its biologically

active forms "when folic acid is consumed at levels higher than the Tolerable Upper Intake Level (1 mg/d for adults)."[7]

Overview of drugs that interfere with folate reactions

A number of drugs interfere with the biosynthesis of folic acid and THF. Among them are the dihydrofolate reductase inhibitors such as trimethoprim, pyrimethamine, and methotrexate; thesulfonamides (competitive inhibitors of 4-aminobenzoic acid in the reactions of dihydropteroate synthetase).

Valproic acid, one of the most commonly prescribed anticonvulsants that is also used to treat certain psychological conditions, is a known inhibitor of folic acid, and as such, has been shown to cause neural tube defects and cases of spina bifida and cognitive impairment in the newborn. Because of this considerable risk, those mothers who must continue to use valproic acid or its derivatives during pregnancy to control their condition (as opposed to stopping the drug or switching to another drug or to a lesser dose) should take folic acid supplements under the direction and guidance of their health care providers.

The National Health and Nutrition Examination Survey (NHANES III 1988–91) and the Continuing Survey of Food Intakes by Individuals (1994–96 CSFII) indicated most adults did not consume adequate folate.[85][86] However, the folic acid fortification program in the United States has increased folic acid content of commonly eaten foods such as cereals and grains, and as a result, diets of most adults now provide recommended amounts of folate equivalents.[87]

Dietary fortification

See also: Food fortification

Folic acid fortification is a process where folic acid is added to flour with the intention of promoting public health through increasing blood folate levels in the populace. In the USA, food is fortified with folic acid, only one of the many naturally-occurring forms of folate, and a substance contributing only a minor amount to the folates in natural foods.[63]

Since the discovery of the link between insufficient folic acid and neural tube defects, governments and health organizations worldwide have made recommendations concerning folic acid*supplementation* for women intending to become pregnant.

Fortification is controversial, with issues having been raised concerning individual liberty,[63] as well as the health concerns described in the Toxicity section above. In the USA, there is concern that the federal government mandates fortification, but does not provide monitoring of potential undesirable effects of fortification.[63]

76 countries worldwide require mandatory folic acid fortification of at least one major cereal grain, with nearly all fortifying at least wheat flour, according to November 2013 data from the Flour Fortification Initiative.[88] These countries are:

Antigua and Barbuda, Argentina, Australia, Bahamas, Bahrain, Barbados, Belize, Benin, Bolivia (Plurinational State of), Brazil, Burkina Faso, Cameroon, Canada, Chile, Colombia, Costa Rica, Cote d'Ivoire, Cuba, Dominica, Dominican Republic, Ecuador, Egypt, El Salvador, Fiji, Ghana, Grenada, Guatemala, Guinea, Guyana, Haiti, Honduras, Indonesia, Iran (Islamic Republic of), Iraq, Jamaica, Jordan, Kazakhstan, Kenya, Kosovo, Kuwait, Kyrgyzstan, Liberia, Mali, Mauritania, Mexico, Morocco, Nepal, Nicaragua, Niger, Nigeria, Oman, Palestine (Occupied Territory), Panama, Papua New Guinea, Paraguay, Peru, Republic of Moldova, Rwanda, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Saudi Arabia, Senegal, Sierra Leone, Solomon Islands, South Africa, Suriname, Tanzania (United Republic of), Togo, Trinidad and Tobago, Turkmenistan, Uganda, United States of America, Uruguay, Uzbekistan, and Yemen.[88]

As of November 2013, no EU country has mandated folic acid fortification.[88]

Australia

There has been previous debate in Australia regarding the inclusion of folic acid in products such as bread and flour.[89]

Australia and New Zealand have jointly agreed to fortification though the Food Standards Australia New Zealand. Australia will fortify all flour from 18 September 2009.[90] Although the food standard covers both Australia and New Zealand, an Australian government official has stated it is up to New Zealand to decide whether to implement it there, and they will watch with interest.[91]

The requirement is 0.135 mg of folate per 100g of bread.

Canada

In 2003, a Hospital for Sick Children, University of Toronto research group published findings showing the fortification of flour with folic acid in Canada has resulted in a dramatic decrease in neuroblastoma, an early and very dangerous cancer in young children.[92] In 2009, further evidence from McGill University showed a 6.2% decrease per year in the birth prevalence of severe congenital heart defects.[93]

Folic acid used in fortified foods is a synthetic form called pteroylmonoglutamate.[94] It is in its oxidized state and contains only one conjugated glutamate residue.[94] Folic acid therefore enters via a different carrier system from naturally occurring folate, and this may have different effects on folate binding proteins and its transporters.[95] Folic acid has a higher bioavailability than natural folates and are rapidly absorbed across the intestine,[94] therefore it is important to consider the Dietary Folate Equivalent (DFE) when calculating one's intake. Natural occurring folate is equal to 1 DFE, however 0.6 µg of folic acid is equal to 1 DFE.

Folic acid food fortification became mandatory in Canada in 1998, with the fortification of 150 µg of folic acid per 100 grams of enriched flour and uncooked cereal grains.[96] The purpose of fortification was to decrease the risk of neural tube defects in newborns.[96] It is important to fortify grains because it is a widely eaten food and the neural tube closes in the first four weeks of gestation, often before many women even know they are pregnant. Canada's fortification program has been successful with a decrease of neural tube defects by 19% since its introduction.[97] A seven-province study from 1993 to 2002 showed a reduction of 46% in the overall rate of neural tube defects after folic acid fortification was introduced in Canada.[98] The fortification program was estimated to raise a person's folic acid intake level by 70–130 µg/day, however an increase of almost double that amount was actually observed.[97] This could be from the fact that many foods are over fortified by 160–175% the predicted value.[97] In addition, much of the elder population take supplements that adds 400 µg to their daily folic acid intake. This is a concern because 70–80% of the population have detectable levels of unmetabolized folic acid in their blood and high intakes can accelerate the growth of preneoplasmic lesions.[99] It is still unknown the amount of folic acid supplementation that might cause harm.[96]

Supplementation promotion

According to a Canadian survey, 58% of women said they took a folic acid containing multivitamin or a folic acid supplement as early as three months before becoming pregnant. Women in higher income households and with more years of school education are using more folic acid supplements before pregnancy. Women with planned pregnancies and who are over the age of 25 are more likely to use folic acid supplement. Canadian public health efforts are focused on promoting awareness of the importance of folic acid supplementation for all women of childbearing age and decreasing socio-economic inequalities by providing practical folic acid support to vulnerable groups of women.[98]

New Zealand

New Zealand was planning to fortify bread (excluding organic and unleavened varieties) from 18 September 2009, but has opted to wait until more research is done.[90]

The Association of Bakers [100] and the Green Party [101] have opposed mandatory fortification, describing it as "mass medication". Food Safety Minister Kate Wilkinson reviewed the decision to

fortify in July 2009, citing links between overconsumption of folate with cancer .[102] The New Zealand Government is reviewing whether it will continue with the mandatory introduction of folic acid to bread.[103]

United Kingdom

There has been previous debate in the United Kingdom regarding the inclusion of folic acid in products such as bread and flour.[104] While the Food Standards Agency has recommended folic acid fortification,[105][106][107] and wheat flour is fortified with iron,[88] folic acid fortification of wheat flour is allowed voluntarily rather than required.

United States

The United States Public Health Service recommends an extra 0.4 mg/day for newly pregnant women, which can be taken as a pill. However, many researchers believe supplementation in this way can never work effectively enough, since about half of all pregnancies in the U.S. are unplanned, and not all women will comply with the recommendation. Approximately 53% of the US population uses dietary supplements and 35% uses dietary supplements containing folic acid.[108]Men consume more folate (in dietary folate equivalents) than women, and non-Hispanic whites have higher folate intakes than Mexican Americans and non-Hispanic blacks.[108] Twenty-nine percent of black women have inadequate intakes of folate.[108] The age group consuming the most folate and folic acid is the >50 group.[108] 5% of the population exceeds the Tolerable Upper Intake Level.[108]

In 1996, the United States Food and Drug Administration (FDA) published regulations requiring the addition of folic acid to enriched breads, cereals, flours, corn meals, pastas, rice, and other grain products.[109][110] This ruling took effect on January 1, 1998, and was specifically targeted to reduce the risk of neural tube birth defects in newborns.[111] There are concerns that the amount of folate added is insufficient .[112] In October 2006, the Australian press claimed that U.S. regulations requiring fortification of grain products were being interpreted as disallowing fortification in non-grain products, specifically Vegemite (an Australian yeast extract containing folate). The FDA later said the report was inaccurate, and no ban or other action was being taken against Vegemite.[113]

As a result of the folic acid fortification program, fortified foods have become a major source of folic acid in the American diet.[10] The Centers for Disease Control and Prevention in Atlanta, Georgia used data from 23 birth defect registries covering about half of United States births, and extrapolated their findings to the rest of the country. These data indicate since the addition of folic acid in grain-based foods as mandated by the FDA, the rate of neural tube defects dropped by 25% in the United States.[114] The results of folic acid fortification on the rate of neural tube defects in Canada have also been positive, showing a 46% reduction in prevalence of NTDs;[115] the magnitude of reduction was proportional to the prefortification rate of NTDs, essentially removing geographical variations in rates of NTDs seen in Canada before fortification.

When the U.S. Food and Drug Administration set the folic acid fortification regulation in 1996, the projected increase in folic acid intake was 100 µg/d.[116] Data from a study with 1480 subjects showed that folic acid intake increased by 190 µg/d and total folate intake increased by 323 µg dietary folate equivalents (DFE)/d.[116] Folic acid intake above the upper tolerable intake level (1000 µg folic acid/d) increased only among those individuals consuming folic acid supplements as well as folic acid found in fortified grain products.[116] Taken together, folic acid fortification has led to a bigger increase in folic acid intake than first projected.[116]

See also

- Levomefolic acid

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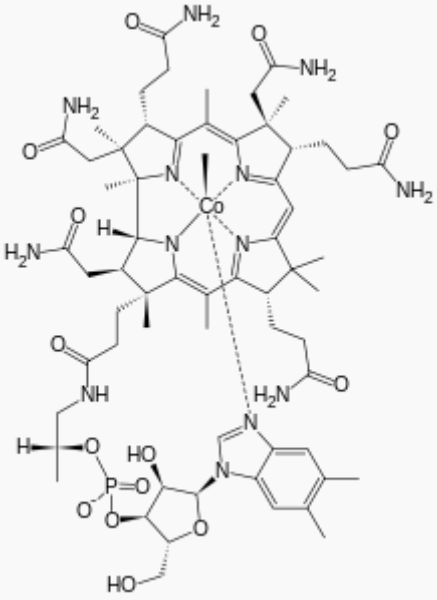
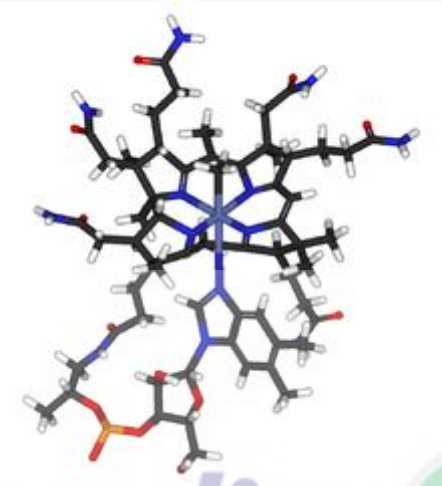
Methylcobalamin

Methylcobalamin





Systematic (IUPAC) name	
carbanide; cobalt(3+);	
Clinical data	
AHFS/Drugs.com	International Drug Names
Legal status	OTC (US)
Routes	oral,sublingual,injection.
Identifiers	
CAS number	13422-55-4
ATC code	B03BA05
PubChem	CID 6436232
UNII	BR1SN1JS2W
ChEMBL	CHEMBL1697757
Chemical data	

Formula	$C_{63}H_{91}CoN_{13}O_{14}P$
Mol. mass	1344.40 g/mol

Methylcobalamin (mecobalamin, MeCbl, or MeB_{12}) is a cobalamin, a form of vitamin B_{12}. It differs from cyanocobalamin in that the cyanide is replaced by a methyl group.[1] Methylcobalamin features an octahedral cobalt(III) centre. Methylcobalamin can be obtained as bright red crystals.[2] From the perspective of coordination chemistry, methylcobalamin is notable as a rare example of a compound that contains metal-alkyl bonds. Nickel-methyl intermediates have been proposed for the final step of methanogenesis.

Methylcobalamin is equivalent physiologically to vitamin B_{12}, and can be used to prevent or treat pathology arising from a lack of vitamin B_{12} (vitamin B12 deficiency), such as pernicious anemia.

Methylcobalamin is also used in the treatment of peripheral neuropathy, diabetic neuropathy, and as a preliminary treatment for amyotrophic lateral sclerosis.

Production

Methylcobalamin can be produced in the laboratory by reducing cyanocobalamin with sodium borohydride in alkaline solution, followed by the addition of methyl iodide.[2]

Functions

This vitamer is one of two active coenzymes used by vitamin B_{12}-dependent enzymes and is the specific vitamin B_{12} form used by 5-methyltetrahydrofolate-homocysteine methyltransferase (MTR), also known as methionine synthase.[*citation needed*]

Methylcobalamin participates in the Wood-Ljungdahl pathway, which is a pathway by which some organisms utilize carbon dioxide as their source of organic compounds. In this pathway, methylcobalamin provides the methyl group that couples to carbon monoxide (derived from CO_2) to afford acetyl-CoA. Acetyl-CoA is a derivative of acetic acid that is converted to more complex molecules as required by the organism.[3]

Methylcobalamin is produced by some bacteria. It plays an important role in the environment. In the environment, it is responsible for the biomethylation of certain heavy metals. For example, the highly toxic methylmercury is produced by the action of methylcobalamin.[4] In this role, methylcobalamin serves as a source of "CH_3^+".

See also

- Cobamamide
- Cyanocobalamin
- Hydroxocobalamin
- Vitamin B12

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2. ^ a b David Dophin. Preparation of the Reduced Forms of Vitamin B_{12} and of Some Analogs of the Vitamin B_{12} Coenzyme Containing a Cobalt-Carbon Bond. *D.B. McCormick and L.D. Wright, Eds*. 1971;Vol. XVIII:34-54.
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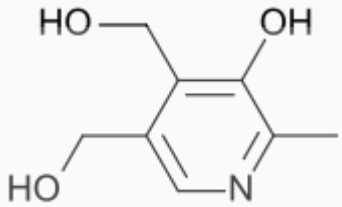
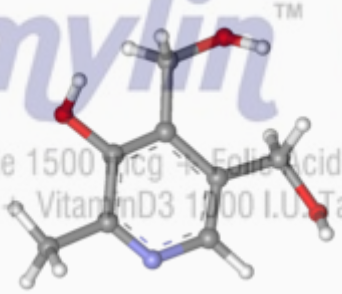
Pyridoxine

Pyridoxine[1]


IUPAC name 4,5-Bis(hydroxymethyl)-2-methylpyridin-3-ol

Identifiers	
CAS number	65-23-6 , 58-56-0 (HCl)
PubChem	1054
ChemSpider	1025
DrugBank	DB00165
KEGG	D08454
ChEBI	CHEBI:16709
ChEMBL	CHEMBL1364
ATC code	A11HA02
Jmol-3D images	Image 1

SMILES

CC1=NC=C(C(=C1O)CO)CO

InChI
InChI=1S/C8H11NO3/c1-5-8(12)7(4-11)6(3-10)2-9-5/h2,10-12H,3-4H2,1H3
Key: LXNHXLLTXMVWPM-UHFFFAOYSA-N

Properties	
Molecular formula	$C_8H_{11}NO_3$
Molar mass	169.18 g mol^{-1}
Melting point	159-162 °C

Except where noted otherwise, data are given for materials in their standard state (at 25 °C (77 °F), 100 kPa)

Pyridoxine is one of the compounds that can be called vitamin B_6, along with pyridoxal and pyridoxamine. It differs from pyridoxamine by the substituent at the '4' position. Its hydrochloride saltpyridoxine hydrochloride is often used.

It is on the World Health Organization's List of Essential Medicines, a list of the most important medication needed in a basic health system.[2]

Medicinal uses

Pyridoxine is given to patients taking isoniazid (INH) to combat the toxic side effects of the drug. It is given to people on isoniazide to prevent peripheral neuropathy and CNS effects that are associated with the use of INH.

Pyridoxine deficiency can lead to sideroblastic anemia.

It is also essential for patients with extremely rare pyridoxine-dependent epilepsy, thought to be caused by mutations in the ALDH7A1 gene.

In one form of homocystinuria, activity of the deficient enzyme can be enhanced by the administration of large doses of pyridoxine (100-1000 mg/day).

Vitamin B_6 can be compounded into a variety of different dosage forms. It can be used orally as a tablet, capsule, or solution. It can also be used as a nasal spray or for injection when in its solution form.

Vitamin B_6 is usually safe at regular intakes. However, vitamin B_6 can cause neurological disorders, such as loss of sensation in legs and imbalance, when taken in high doses over a long period of time. Vitamin B_6 toxicity can damage sensory nerves, leading to numbness in the hands and feet as well as difficulty walking. Symptoms of a pyridoxine overdose may include poor coordination, staggering, numbness, decreased sensation to touch, temperature, and vibration, and tiredness for up to six months.[3] One study reported that over a 6-month period or longer, 21% of women taking doses greater than 50 mg daily experienced neurological toxicity.[4] The effect of doses below 50 mg was not reported. Pyridoxine's fetal safety is "A" in Briggs' Reference Guide to Fetal and Neonatal Risk.[5] Its also used to treat a Vitamin B6 deficiency.

Chemistry

It is based on a pyridine ring, with hydroxyl, methyl, and hydroxymethyl substituents. It is converted to the biologically active form pyridoxal 5-phosphate.

Function in the body

Vitamin B_6 assists in the balancing of sodium and potassium as well as promoting red blood cell production. It is linked to cardiovascular health by decreasing the formation ofhomocysteine. Pyridoxine may help balance hormonal changes in women and aid the immune system.[6] Lack of pyridoxine may cause anemia, nerve damage, seizures, skin problems, and sores in the mouth.[7]

It is required for the production of the monoamine neurotransmitters serotonin, dopamine, norepinephrine and epinephrine, as it is the precursor to pyridoxal phosphate: cofactor for the enzymearomatic amino acid decarboxylase. This enzyme is responsible for converting the precursors 5-hydroxytryptophan (5-HTP) into serotonin and melatonin, and levodopa (L-DOPA) into dopamine,noradrenaline and adrenaline. As such it has been implicated in the treatment of depression and anxiety.

Natural sources

Fish, soybeans, avocado, lima beans, chicken, bananas, cauliflower, green peppers, potatoes, spinach, raisins, brewer's yeast, blackstrap molasses, liver, kidney, heart. [8]

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