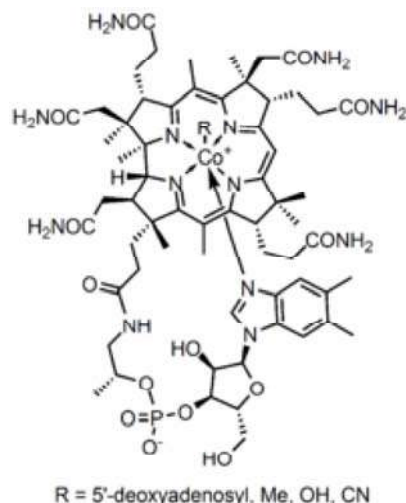


Vitamin B₁₂

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Vitamin B12



R = 5'-deoxyadenosyl, Me, OH, CN

Clinical data

AHFS/Drugs.com Monograph (https://www.drugs.com/monograph/vitamin_b12.html)

Routes of administration oral, IV, IM, intranasal

ATC code B03BA01 (WHO (http://www.whocc.no/atc_ddd_index/?code=B03BA01))

Legal status

Legal status UK: POM (Prescription only)
US: OTC

Pharmacokinetic data

Bioavailability Readily absorbed in distal half of the ileum

Protein binding Very high to specific transcobalamins plasma proteins
Binding of hydroxocobalamin is slightly higher than cyanocobalamin.

Metabolism hepatic

Biological half-life Approximately 6 days
(400 days in the liver)

Excretion Renal

Identifiers

IUPAC name

CAS Number 68-19-9 (<http://www.commonchemistry.org/ChemicalDetail.aspx?ref=68-19-9>) ✓

PubChem (CID) 5479203 (<https://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=5479203>)

DrugBank DB00115 (<https://www.drugbank.ca/drugs/DB00115>) ✗

ChemSpider

	10469504 (http://www.chemspider.com/Chemical-Structure.10469504.html) ✓
KEGG	D00166 (http://www.kegg.jp/entry/D00166) ✓
ChEMBL	CHEMBL2110563 (https://www.ebi.ac.uk/chembl/db/index.php/compound/inspect/CHEMBL2110563) ✗
Chemical and physical data	
Formula	C ₆₃ H ₈₈ CoN ₁₄ O ₁₄ P
Molar mass	1355.37 g/mol
3D model (Jmol)	Interactive image (http://chemapps.stolaf.edu/jmol/jmol.php?model=NC%28%3DO%29C%5BC%40%40%5D8%28C%29%5BC%40H%5D%28CCC%28N%29%3DO%29C%3D2%2FN%3DC8%2FC%28%2FC%29%3DC1%2F%5BC%40%40H%5D%28CCC%28N%29%3DO%29%5BC%40%5D%28C%29%28CC%28N%29%3DO%29%5BC%40%40%5D%28C%29%28N1%5BCo%2B%5DC%23N%29%5BC%40%40H%5D7%2FN%3DC%28C%28%5CC%29%3DC3%2FN%3DC%28%2FC%3D2%29C%28C%29%28C%29%5BC%40%40H%5D3CCC%28N%29%3DO%29%5BC%40%5D%28C%29%28CCC%28%3DO%29NCC%28C%29OP%28%5BO-%5D%29%28%3DO%29O%5BC%40%40H%5D6%5BC%40%40H%5D%28CO%29O%5BC%40H%5D%28n5cnc4cc%28C%29c%28C%29cc45%29%5BC%40%40H%5D6O%29%5BC%40H%5D7CC%28N%29%3DO)
SMILES	
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	✗✓ (what is this?) (verify)

Vitamin B₁₂, **vitamin B12** or **vitamin B-12**, also called **cobalamin**, is a water-soluble vitamin that has a key role in the normal functioning of the brain and nervous system, and the formation of red blood cells. It is one of eight B vitamins. It is involved in the metabolism of every cell of the human body, especially affecting DNA synthesis, fatty acid and amino acid metabolism.^[1] No fungi, plants, nor animals (including humans) are capable of producing vitamin B₁₂. Only bacteria and archaea have the enzymes needed for its synthesis. Proved sources of B₁₂ are animal products (meat, fish, dairy products) and supplements. Some research states that certain non-animal products possibly can be a natural source of B₁₂ because of bacterial symbiosis. B₁₂ is the largest and most structurally complicated vitamin and can be produced industrially only through a bacterial fermentation-synthesis. This synthetic B₁₂ is used to fortify foods and sold as a dietary supplement.

Vitamin B₁₂ consists of a class of chemically related compounds (vitamers), all of which show pharmacological activity. It contains the biochemically rare element cobalt (chemical symbol **Co**) positioned in the center of a planar tetra-pyrrole ring called a corrin ring. The vitamer is produced by bacteria as hydroxocobalamin, but conversion between different forms of the vitamin occurs in the body after consumption.

Vitamin B₁₂ was discovered^[2] as a result of its relationship to the disease pernicious anemia, an autoimmune disease in which parietal cells of the stomach responsible for secreting intrinsic factor are destroyed; these cells are also responsible for secreting acid in the stomach. Because intrinsic factor is crucial for the normal absorption of B₁₂, its lack in the presence of pernicious anemia causes a vitamin B₁₂ deficiency. Many other subtler kinds of vitamin B₁₂ deficiency and their biochemical effects have since been elucidated.^[3]

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Methylcobalamin (shown) is a form of vitamin B₁₂. Physically it resembles the other forms of vitamin B₁₂, occurring as dark red crystals that freely form cherry-colored transparent solutions in water.

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Medical uses

Vitamin B₁₂ is used to treat vitamin B₁₂ deficiency, cyanide poisoning, and hereditary deficiency of transcobalamin II.^[4] It is given as part of the Schilling test for detecting pernicious anemia.^[4]

For cyanide poisoning, a large amount of hydroxocobalamin may be given intravenously and sometimes in combination with sodium thiosulfate.^[5] The mechanism of action is straightforward: the hydroxycobalamin hydroxide ligand is displaced by the toxic cyanide ion, and the resulting harmless B₁₂ complex is excreted in urine. In the United States, the Food and Drug Administration approved (in 2006) the use of hydroxocobalamin for acute treatment of cyanide poisoning.^[6]

Dietary Reference Intake

The Food and Nutrition Board of the U.S. Institute of Medicine updated Estimated Average Requirements (EARs) and Recommended Dietary Allowances (RDAs) for vitamin B₁₂ in 1998. The current EAR for vitamin B₁₂ for women and men ages 14 and up is 2.0 µg/day; the RDA is 2.4 µg/day. RDAs are higher than EARs so as to identify amounts that will cover people with higher than average requirements. RDA for pregnancy equals 2.6 µg/day. RDA for lactation equals 2.8 µg/day. For infants up to 12 months the Adequate Intake (AI) is 0.4-0.5 µg/day. and for children ages 1–13 years the RDA increases with age from 0.9 to 1.8 µg/day. Because 10 to 30 percent of older people may be unable to effectively absorb vitamin B₁₂ naturally occurring in foods, it is advisable for those older than 50 years to meet their RDA mainly by consuming foods fortified with vitamin B₁₂ or a supplement containing vitamin B₁₂.

As for safety, the Food and Nutrition Board of the U.S. Institute of Medicine sets Tolerable Upper Intake Levels (known as ULs) for vitamins and minerals when evidence is sufficient. In the case of vitamin B₁₂ there is no UL, as there is no human data for adverse effects from high doses. The European Food Safety Authority reviewed the same safety question and also reached the conclusion that there was not sufficient evidence to set a UL for vitamin B₁₂.^[7] Collectively the EARs, RDAs and ULs are referred to as Dietary Reference Intakes.^[8]

For U.S. food and dietary supplement labeling purposes the amount in a serving is expressed as a percent of Daily Value (%DV). For vitamin B₁₂ labeling purposes 100% of the Daily Value was 6.0 µg, but as of May 2016 it has been revised downward to 2.4 µg. A table of the pre-change adult Daily Values is provided at Reference Daily Intake. Food and supplement companies have until July 2018 to comply with the change.

Controversial sources in algae

The UK Vegan Society, the Vegetarian Resource Group, and the Physicians Committee for Responsible Medicine, among others, recommend that vegans either consistently eat B₁₂-fortified foods or take a daily or weekly B₁₂ supplement to meet the recommended intake.^{[9][10][11]}

It is important for vegans, whose food provides few sources of B₁₂, and anyone else wishing to obtain B₁₂ from food sources other than animals, to consume foods that contain little or no pseudovitamin-B₁₂ and are high in biologically active B₁₂.

So-called pseudovitamin-B₁₂ refers to B₁₂-like analogues that are biologically inactive in humans and yet found to be present alongside B₁₂ in humans,^[12] many food sources (including animals^[13]), and possibly supplements and fortified foods.^[14] In most cyanobacteria, including *Spirulina*, and some algae, such as dried Asakusa-nori (*Porphyra tenera*), pseudovitamin-B₁₂ is found to predominate.^[15]

There have been no significant human trials of sufficient size to demonstrate enzymatic activity of B₁₂ from nonbacterial sources, such as *Chlorella* and edible sea algae (seaweeds, such as lavers), although chemically some of these sources have been reported to contain B₁₂ that seems chemically similar to the active vitamin.^[16]

Deficiency

Vitamin B₁₂ deficiency can potentially cause severe and irreversible damage, especially to the brain and nervous system.^[17] At levels only slightly lower than normal, a range of symptoms such as fatigue, depression, and poor memory may be experienced.^[3] Vitamin B₁₂ deficiency can also cause symptoms of mania and psychosis.^{[18][19]}

Vitamin B₁₂ deficiency is most commonly caused by low intakes, but can also result from malabsorption, certain intestinal disorders, low presence of binding proteins, and use of certain medications. Vitamin B₁₂ is rare from plant sources, so vegetarians are most likely to suffer from vitamin B₁₂ deficiency. Infants are at a higher risk of vitamin B₁₂ deficiency if they were born to vegetarian mothers. The elderly who have diets with limited meat or animal products are vulnerable populations as well.^[20]

Vitamin B₁₂ deficiency can manifest itself as anemia. In some cases, deficiency can cause permanent neurological damage. Recent studies show depression is associated with vitamin B₁₂ deficiency; sufficient vitamin B₁₂ levels are independently associated with a decreased risk of depression and better cognitive performance adjusted for confounders.

Vitamin B₁₂ is a co-substrate of various cell reactions involved in methylation synthesis of nucleic acid and neurotransmitters. Synthesis of the trimonoamine neurotransmitters can enhance the effects of a traditional antidepressant.^[21] The intracellular concentrations of vitamin B₁₂ can be inferred through the total plasma concentration of homocysteine, which can be converted to methionine through an enzymatic reaction that uses 5-methyltetrahydrofolate as the methyl donor group. Consequently, the plasma concentration of homocysteine falls as the intracellular concentration of vitamin B₁₂ rises. The active metabolite of vitamin B₁₂ is required for the methylation of homocysteine in the production of methionine, which is involved in a number of biochemical processes including the monoamine neurotransmitters metabolism. Thus, a deficiency in vitamin B₁₂ may impact the production and function of those neurotransmitters.^[22]

Sources

Animal sources

Vitamin B₁₂ is found in most animal-derived foods, including fish and shellfish, meat (especially liver), poultry, eggs, milk, and milk products.^[3] The bioavailability from eggs is less than 9%, compared to 40% to 60% from fish, fowl and meat.^[23] An NIH fact sheet lists a variety of animal food sources of B₁₂.^[3]

Fortified foods

Foods fortified with B₁₂ are also dietary sources of the vitamin. Foods for which B₁₂-fortified versions are widely available include breakfast cereals, soy products, energy bars, and nutritional yeast. The UK Vegan Society, the Vegetarian Resource Group, and the Physicians Committee for Responsible Medicine, among others, recommend that every vegan who is not consuming adequate B₁₂ from fortified foods takes supplements.^{[24][10][11]} Reputable manufacturers of fortified foods and dietary supplements include an overage (excess) in their formulas so that the products still contain the labeled amounts at the end of shelf life.

Supplements

Vitamin B₁₂ is an ingredient in multi-vitamin pills and in some countries used to enrich grain-based foods such as bread and pasta. In the U.S. non-prescription products can be purchased providing up to 5000 µg/serving, and it is a common ingredient in energy drinks and energy shots, usually at many times the recommended dietary allowance of B₁₂. The vitamin can also be a prescription product via injection or other means.

The sublingual route, in which B₁₂ is presumably or supposedly taken in more directly under the tongue, has not proven to be necessary or helpful, even though a number of lozenges, pills, and even a lollipop designed for sublingual absorption are being marketed. A 2003 study found no significant difference in absorption for serum levels from oral versus sublingual delivery of 0.5 mg of cobalamin.^[25] Sublingual

methods of replacement are effective only because of the typically high doses (0.5 mg), which are swallowed, not because of placement of the tablet. As noted below, such very high doses of oral B₁₂ may be effective as treatments, even if gastrointestinal tract absorption is impaired by gastric atrophy (pernicious anemia).

Injection and patches are sometimes used if digestive absorption is impaired, but there is evidence that this course of action may not be necessary with modern high-potency oral supplements (such as 0.5–1 mg or more). Even pernicious anemia can be treated entirely by the oral route.^{[26][27][28]} These supplements carry such large doses of the vitamin that 1% to 5% of high oral doses of free crystalline B₁₂ is absorbed along the entire intestine by passive diffusion.

If the patient has inborn errors in the methyltransfer pathway (cobalamin C disease, combined methylmalonic aciduria and homocystinuria), treatment with intravenous, intramuscular hydroxocobalamin or transdermal B₁₂ is needed.^{[29][30][31][32][33]}

Non-cyanide forms as supplements

Recently sublingual methylcobalamin has become available in 5 mg tablets. The metabolic fate and biological distribution of methylcobalamin are expected to be similar to that of other sources of vitamin B₁₂ in the diet.^[34] No cyanide is released with methylcobalamin. The amount of cyanide (20 µg cyanide in a 1,000 µg cyanocobalamin tablet) is less than daily consumption from food. Safety of all forms of the vitamin is well established.^[34]

Controversial sources

Besides certain fermented foods,^{[35][36]} there are few known plant, fungus or algae sources of biologically active B₁₂ and none of these have been subjected to human trials.

Spirulina and dried Asakusa-nori (*Porphyra tenera*) have been found to contain mostly pseudovitamin-B₁₂ (see Controversial sources in algae section) instead of biologically active B₁₂.^{[15][37]}

Elevated plasma B₁₂ (cobalamin) levels

Elevated levels of serum B₁₂ or cobalamin (above about 600 pmol/L) in the absence of supplementation may be a diagnostic sign of serious disease. In such cases B₁₂ is thought to be only a marker for disease, and not a causal agent.



Hydroxocobalamin injection USP (1000 µg/mL) is a clear red liquid solution of hydroxocobalamin which is available in a 30 mL brown glass multidose vial packaged in a paper box. Shown is 500 µg B₁₂ (as 1/2 cc) drawn up in a 1/2 cc U-100 27 gauge x 1/2" insulin syringe, as prepared for subcutaneous injection.

One cause of elevated plasma B₁₂ (cobalamin) is general liver disease, since hepatic cytolysis releases B₁₂, and the affected liver shows decreased cobalamin clearance. Thus, acute hepatitis, cirrhosis, hepatocellular carcinoma and metastatic liver disease can also be accompanied by an increase in circulating cobalamin. Elevated B₁₂ levels have been suggested as a predictor of ICU mortality risk, but a recent study of this found that "[e]levated B₁₂ levels are not a significant predictor of mortality after ICU admission when liver function is controlled for, and may instead be a proxy for poor liver function." [38]

A second group of non-supplemented patients with high cobalamin levels have them due to enhanced production of the plasma B₁₂ transporters haptocorrin and transcobalamin II [39] This happens in hematologic disorders like chronic myelogenous leukemia, promyelocytic leukemia, polycythemia vera and also the hypereosinophilic syndrome. Increased cobalamin levels are one of the diagnostic criteria for the latter two diseases.

A third group of non-supplemented patients with high cobalamin levels (> 600 pmol/L) may be at immediate (mostly within one year of testing) higher risk for new diagnosis of certain smoking and alcohol-related cancers which are non-hematologic. In a study of 333,000 persons in Denmark, those with elevated B₁₂ had a three to six times higher standard incidence ratio, with respect to those with normal B₁₂ levels, for later development of certain types of cancer. [40]

Thus, one review states: "Altogether it can be concluded that an observed elevation of cobalamin in blood merits a full diagnostic work up to assess the presence of disease." [41]

Interactions

Vitamin B₁₂ may interact with prescription drugs. [3]

Examples

- H₂-receptor antagonists: include cimetidine (Tagamet), famotidine (Pepcid), nizatidine (Axid), and ranitidine (Zantac). Reduced secretion of gastric acid and pepsin produced by H₂ blockers can reduce absorption of protein-bound (dietary) vitamin B₁₂, but not of supplemental vitamin B₁₂. Gastric acid is needed to release vitamin B₁₂ from protein for absorption. Clinically significant vitamin B₁₂ deficiency and megaloblastic anemia are unlikely, unless H₂ blocker therapy is prolonged (2 years or more), or the person's diet is poor. It is also more likely if the person is rendered achlorhydric (with complete absence of gastric acid secretion), which occurs more frequently with proton pump inhibitors than H₂ blockers. Vitamin B₁₂ levels should be monitored in people taking high doses of H₂ blockers for prolonged periods.
- Metformin (Glucophage): Metformin may reduce serum folic acid and vitamin B₁₂ levels. Long-term use of metformin substantially increases the risk of B₁₂ deficiency and (in those patients who become deficient) hyperhomocysteinemia, which is "an independent risk factor for cardiovascular disease, especially among individuals with type 2 diabetes". [42] There are also rare reports of megaloblastic anemia in people who have taken metformin for five years or more. Reduced serum levels of vitamin B₁₂ occur in up to 30% of people taking metformin chronically. [43][44] Clinically

significant deficiency is not likely to develop if dietary intake of vitamin B₁₂ is adequate. Deficiency can be corrected with vitamin B₁₂ supplements even if metformin is continued. The metformin-induced malabsorption of vitamin B₁₂ is reversible by oral calcium supplementation.^[45] The general clinical significance of metformin upon B₁₂ levels is as yet unknown.^[46]

- Proton pump inhibitors (PPIs): The PPIs include omeprazole (Prilosec, Losec), lansoprazole (Prevacid), rabeprazole (Aciphex), pantoprazole (Protonix, Pantoloc), and esomeprazole (Nexium). The reduced secretion of gastric acid and pepsin produced by PPIs can reduce absorption of protein-bound (dietary) vitamin B₁₂, but not supplemental vitamin B₁₂. Gastric acid is needed to release vitamin B₁₂ from protein for absorption. Reduced vitamin B₁₂ levels may be more common with PPIs than with H₂-blockers, because they are more likely to produce achlorhydria (complete absence of gastric acid secretion). Clinically significant vitamin B₁₂ deficiency is unlikely, unless PPI therapy is prolonged (2 years or more) or dietary vitamin intake is low. Vitamin B₁₂ levels should be monitored in people taking high doses of PPIs for prolonged periods.

Structure

B₁₂ is the most chemically complex of all the vitamins. The structure of B₁₂ is based on a corrin ring, which is similar to the porphyrin ring found in heme, chlorophyll, and cytochrome. The central metal ion is cobalt. Four of the six coordination sites are provided by the corrin ring, and a fifth by a dimethylbenzimidazole group. The sixth coordination site, the center of reactivity, is variable, being a cyano group (-CN), a hydroxyl group (-OH), a methyl group (-CH₃) or a 5'-deoxyadenosyl group (here the C5' atom of the deoxyribose forms the covalent bond with Co), respectively, to yield the four B₁₂ forms mentioned below. Historically, the covalent C-Co bond is one of the first examples of carbon-metal bonds to be discovered in biology. The hydrogenases and, by necessity, enzymes associated with cobalt utilization, involve metal-carbon bonds.^[47]

Vitamin B₁₂ is a generic descriptor name referring to a collection of cobalt and corrin ring molecules which are defined by their particular vitamin function in the body. All of the substrate cobalt-corrin molecules from which B₁₂ is made must be synthesized by bacteria. After this synthesis is complete, the human body has the ability (except in rare cases) to convert any form of B₁₂ to an active form, by means of enzymatically removing certain prosthetic chemical groups from the cobalt atom and replacing them with others.

The four forms (vitamers) of B₁₂ are all deeply red colored crystals and water solutions, due to the color of the cobalt-corrin complex.

Cyanocobalamin is one such form, i.e. "vitamer", of B₁₂ because it can be metabolized in the body to an active coenzyme form. The cyanocobalamin form of B₁₂ does not occur in nature normally, but is a byproduct of the fact that other forms of B₁₂ are avid binders of cyanide (-CN) which they pick up in the process of activated charcoal purification of the vitamin after it is made by bacteria in the commercial process. Since the cyanocobalamin form of B₁₂ is easy to crystallize and is not sensitive to air-oxidation,

it is typically used as a form of B₁₂ for food additives and in many common multivitamins. Pure cyanocobalamin possesses the deep pink color associated with most octahedral cobalt(II) complexes and the crystals are well formed and easily grown up to millimeter size.

Hydroxocobalamin is another form of B₁₂ commonly encountered in pharmacology, but which is not normally present in the human body. Hydroxocobalamin is sometimes denoted B_{12a}. This form of B₁₂ is the form produced by bacteria, and is what is converted to cyanocobalamin in the commercial charcoal filtration step of production. Hydroxocobalamin has an avid affinity for cyanide ions and has been used as an antidote to cyanide poisoning. It is supplied typically in water solution for injection. Hydroxocobalamin is thought to be converted to the active enzymic forms of B₁₂ more easily than cyanocobalamin, and since it is little more expensive than cyanocobalamin, and has longer retention times in the body, has been used for vitamin replacement in situations where added reassurance of activity is desired. Intramuscular administration of hydroxocobalamin is also the preferred treatment for pediatric patients with intrinsic cobalamin metabolic diseases, for vitamin B₁₂ deficient patients with tobacco amblyopia (which is thought to perhaps have a component of cyanide poisoning from cyanide in cigarette smoke); and for treatment of patients with pernicious anemia who have optic neuropathy.

Adenosylcobalamin (adoB₁₂) and **methylcobalamin** (MeB₁₂) are the two enzymatically active cofactor forms of B₁₂ that naturally occur in the body. Most of the body's reserves are stored as adoB₁₂ in the liver. These are converted to the other methylcobalamin form as needed.

Synthesis and industrial production

Neither plants nor animals are independently capable of constructing vitamin B₁₂.^[48] Only bacteria and archaea^[49] have the enzymes required for its biosynthesis. The total synthesis of B₁₂ was reported by Robert Burns Woodward^[50] and Albert Eschenmoser in 1972,^{[51][52]} and remains one of the classic feats of organic synthesis. Species from the following genera are known to synthesize B₁₂: *Acetobacterium*, *Aerobacter*, *Agrobacterium*, *Alcaligenes*, *Azotobacter*, *Bacillus*, *Clostridium*, *Corynebacterium*, *Flavobacterium*, *Lactobacillus*, *Micromonospora*, *Mycobacterium*, *Nocardia*, *Propionibacterium*, *Protaminobacter*, *Proteus*, *Pseudomonas*, *Rhizobium*, *Salmonella*, *Serratia*, *Streptomyces*, *Streptococcus* and *Xanthomonas*.

Industrial production of B₁₂ is achieved through fermentation of selected microorganisms.^[53] *Streptomyces griseus*, a bacterium once thought to be a yeast, was the commercial source of vitamin B₁₂ for many years.^{[54][55]} The species *Pseudomonas denitrificans* and *Propionibacterium freudenreichii* *subsp. shermanii* are more commonly used today.^[56] These are frequently grown under special conditions to enhance yield, and at least one company, Rhône-Poulenc of France, which has merged into Sanofi-Aventis, used genetically engineered versions of one or both of these species. Since a number of species of *Propionibacterium* produce no exotoxins or endotoxins and are generally regarded as safe (have been granted GRAS status) by the Food and Drug Administration of the United States, they are presently the FDA-preferred bacterial fermentation organisms for vitamin B₁₂ production.^[57]

The total world production of vitamin B₁₂, by four companies (the French Sanofi-Aventis and three Chinese companies) is said to have been 35 tonnes in 2008.^[58]

See cyanocobalamin for discussion of the chemical preparation of reduced-cobalt vitamin analogs and preparation of physiological forms of the vitamin such as adenosylcobalamin and methylcobalamin.

Mechanism of action

Vitamin B₁₂ functions as a coenzyme, meaning that its presence is required for enzyme-catalyzed reactions.^{[59][60]} Three types of enzymes:

1. Isomerases

Rearrangements in which a hydrogen atom is directly transferred between two adjacent atoms with concomitant exchange of the second substituent, X, which may be a carbon atom with substituents, an oxygen atom of an alcohol, or an amine. These use the adoB₁₂ (adenosylcobalamin) form of the vitamin.

2. Methyltransferases

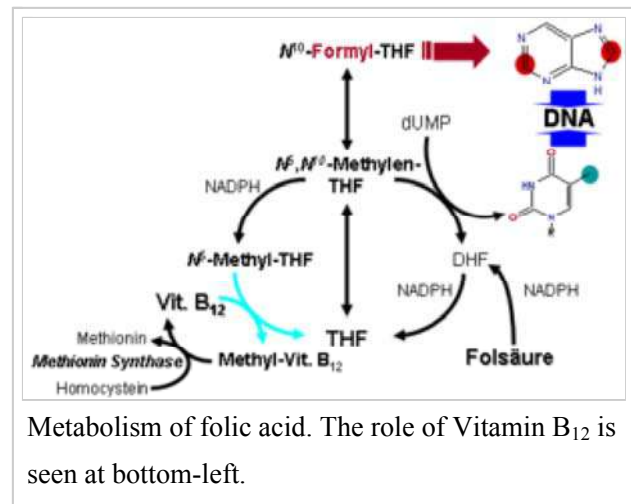
Methyl (-CH₃) group transfers between two molecules. These use MeB₁₂ (methylcobalamin) form of the vitamin.

3. Dehalogenases

Reactions in which a halogen atom is removed from an organic molecule. Enzymes in this class have not been identified in humans.

In humans, two major coenzyme B₁₂-dependent enzyme families corresponding to the first two reaction types, are known. These are typified by the following two enzymes:

1. MUT is an isomerase which uses the AdoB₁₂ form and reaction type 1 to catalyze a carbon skeleton rearrangement (the X group is -C(=O)CoA). MUT's reaction converts MMI-CoA to Su-CoA, an important step in the extraction of energy from proteins and fats (*for more see MUT's reaction mechanism*). This functionality is lost in vitamin B₁₂ deficiency, and can be measured clinically as an increased methylmalonic acid (MMA) level. Unfortunately, an elevated MMA, though sensitive to B₁₂ deficiency, is probably overly sensitive, and not all who have it actually have B₁₂ deficiency. For example, MMA is elevated in 90–98% of patients with B₁₂ deficiency; 20–25% of patients over the age of 70 have elevated levels of MMA, yet 25–33% of them do not have B₁₂ deficiency. For this reason, assessment of MMA levels is not routinely recommended in the elderly. There is no "gold standard" test for B₁₂ deficiency because as a B₁₂ deficiency occurs, serum values may be maintained while tissue B₁₂ stores become depleted. Therefore, serum B₁₂



values above the cut-off point of deficiency do not necessarily indicate adequate B₁₂ status. The MUT function is necessary for proper myelin synthesis (see mechanism below) and is not affected by folate supplementation.

2. MTR, also known as methionine synthase, is a methyltransferase enzyme, which uses the MeB₁₂ and reaction type 2 to transfer a methyl group from 5-methyltetrahydrofolate to homocysteine, thereby generating tetrahydrofolate (THF) and methionine (*for more see MTR's reaction mechanism*).^[61] This functionality is lost in vitamin B₁₂ deficiency, resulting in an increased homocysteine level and the trapping of folate as 5-methyl-tetrahydrofolate, from which THF (the active form of folate) cannot be recovered. THF plays an important role in DNA synthesis so reduced availability of THF results in ineffective production of cells with rapid turnover, in particular red blood cells, and also intestinal wall cells which are responsible for absorption. THF may be regenerated via MTR or may be obtained from fresh folate in the diet. Thus all of the DNA synthetic effects of B₁₂ deficiency, including the megaloblastic anemia of pernicious anemia, resolve if sufficient dietary folate is present. Thus the best-known "function" of B₁₂ (that which is involved with DNA synthesis, cell-division, and anemia) is actually a facultative function which is mediated by B₁₂-conservation of an active form of folate which is needed for efficient DNA production.^[62] Other cobalamin-requiring methyltransferase enzymes are also known in bacteria, such as Me-H4-MPT, coenzyme M methyl transferase.

Enzyme function

If folate is present in quantity, then of the two absolutely vitamin B₁₂-dependent enzyme-family reactions in humans, the MUT-family reactions show the most direct and characteristic secondary effects, focusing on the nervous system (see below). This is because the MTR (methyltransferase-type) reactions are involved in regenerating folate, and thus are less evident when folate is in good supply.

Since the late 1990s, folic acid has begun to be added to fortify flour in many countries, so folate deficiency is now more rare. At the same time, since DNA synthetic-sensitive tests for anemia and erythrocyte size are routinely done in even simple medical test clinics (so that these folate-mediated biochemical effects are more often directly detected), the MTR-dependent effects of B₁₂ deficiency are becoming apparent not as anemia due to DNA-synthetic problems (as they were classically), but now mainly as a simple and less obvious elevation of homocysteine in the blood and urine (homocysteinuria). This condition may result in long term damage to arteries and in clotting (stroke and heart attack), but this effect is difficult to separate from other common processes associated with atherosclerosis and aging.

The specific myelin damage resulting from B₁₂ deficiency, even in the presence of adequate folate and methionine, is more specifically and clearly a vitamin deficiency problem. It has been connected to B₁₂ most directly by reactions related to MUT, which is absolutely required to convert methylmalonyl coenzyme A into succinyl coenzyme A. Failure of this second reaction to occur results in elevated levels of MMA, a myelin destabilizer. Excessive MMA will prevent normal fatty acid synthesis, or it will be incorporated into fatty acid itself rather than normal malonic acid. If this abnormal fatty acid subsequently is incorporated into myelin, the resulting myelin will be too fragile, and demyelination will occur. Although the precise mechanism(s) are not known with certainty, the result is subacute combined

degeneration of central nervous system and spinal cord.^[63] Whatever the cause, it is known that B₁₂ deficiency causes neuropathies, even if folic acid is present in good supply, and therefore anemia is not present.

Vitamin B₁₂-dependent MTR reactions may also have neurological effects, through an indirect mechanism. Adequate methionine (which, like folate, must otherwise be obtained in the diet, if it is not regenerated from homocysteine by a B₁₂ dependent reaction) is needed to make S-adenosyl-methionine (SAdMe), which is in turn necessary for methylation of myelin sheath phospholipids. Although production of SAdMe is not B₁₂ dependent, help in recycling for provision of one adequate substrate for it (the essential amino acid methionine) is assisted by B₁₂. In addition, SAdMe is involved in the manufacture of certain neurotransmitters, catecholamines and in brain metabolism. These neurotransmitters are important for maintaining mood, possibly explaining why depression is associated with B₁₂ deficiency. Methylation of the myelin sheath phospholipids may also depend on adequate folate, which in turn is dependent on MTR recycling, unless ingested in relatively high amounts.

Absorption and distribution

Methyl-B₁₂ is absorbed by two processes. The first is an intestinal mechanism using intrinsic factor through which 1-2 micrograms can be absorbed every few hours. The second is a diffusion process by which approximately 1% of the remainder is absorbed.^[64] The human physiology of vitamin B₁₂ is complex, and therefore is prone to mishaps leading to vitamin B₁₂ deficiency. Protein-bound vitamin B₁₂ must be released from the proteins by the action of digestive proteases in both the stomach and small intestine.^[65] Gastric acid releases the vitamin from food particles; therefore antacid and acid-blocking medications (especially proton-pump inhibitors) may inhibit absorption of B₁₂. In addition some elderly people produce less stomach acid as they age thereby increasing their probability of B₁₂ deficiencies.^[66]

B₁₂ taken in a low-solubility, non-chewable supplement pill form may bypass the mouth and stomach and not mix with gastric acids, but acids are not necessary for the absorption of free B₁₂ not bound to protein; acid is necessary only to recover naturally-occurring vitamin B₁₂ from foods.

R-protein (also known as haptocorrin and cobalophilin) is a B₁₂ binding protein that is produced in the salivary glands. It must wait to bind food-B₁₂ until B₁₂ has been freed from proteins in food by pepsin in the stomach. B₁₂ then binds to the R-protein to avoid degradation of it in the acidic environment of the stomach.^[67]

This pattern of B₁₂ transfer to a special binding protein secreted in a previous digestive step, is repeated once more before absorption. The next binding protein for B₁₂ is intrinsic factor (IF), a protein synthesized by gastric parietal cells that is secreted in response to histamine, gastrin and pentagastrin, as well as the presence of food. In the duodenum, proteases digest R-proteins and release their bound B₁₂,

which then binds to IF, to form a complex (IF/B₁₂). B₁₂ must be attached to IF for it to be efficiently absorbed, as receptors on the enterocytes in the terminal ileum of the small bowel only recognize the B₁₂-IF complex; in addition, intrinsic factor protects the vitamin from catabolism by intestinal bacteria.

Absorption of food vitamin B₁₂ thus requires an intact and functioning stomach, exocrine pancreas, intrinsic factor, and small bowel. Problems with any one of these organs makes a vitamin B₁₂ deficiency possible. Individuals who lack intrinsic factor have a decreased ability to absorb B₁₂. In pernicious anemia, there is a lack of IF due to autoimmune atrophic gastritis, in which antibodies form against parietal cells. Antibodies may alternately form against and bind to IF, inhibiting it from carrying out its B₁₂ protective function. Due to the complexity of B₁₂ absorption, geriatric patients, many of whom are hypoacidic due to reduced parietal cell function, have an increased risk of B₁₂ deficiency.^[68] This results in 80–100% excretion of oral doses in the feces versus 30–60% excretion in feces as seen in individuals with adequate IF.^[68]

Once the IF/B₁₂ complex is recognized by specialized ileal receptors, it is transported into the portal circulation. The vitamin is then transferred to transcobalamin II (TC-II/B₁₂), which serves as the plasma transporter. Hereditary defects in production of the transcobalamins and their receptors may produce functional deficiencies in B₁₂ and infantile megaloblastic anemia, and abnormal B₁₂ related biochemistry, even in some cases with normal blood B₁₂ levels. For the vitamin to serve inside cells, the TC-II/B₁₂ complex must bind to a cell receptor, and be endocytosed. The transcobalamin-II is degraded within a lysosome, and free B₁₂ is finally released into the cytoplasm, where it may be transformed into the proper coenzyme, by certain cellular enzymes (see above).

Investigations into the intestinal absorption of B₁₂ point out that the upper limit of absorption per single oral dose, under normal conditions, is about 1.5 µg: "Studies in normal persons indicated that about 1.5 µg is assimilated when a single dose varying from 5 to 50 µg is administered by mouth. In a similar study Swendseid *et al.* stated that the average maximum absorption was 1.6 µg [...]"^[69] The bulk diffusion process of B₁₂ absorption noted in the first paragraph above, may overwhelm the complex R-factor and IGF-factor dependent absorption, when oral doses of B₁₂ are very large (a thousand or more µg per dose) as commonly happens in dedicated-pill oral B₁₂ supplementation. It is this last fact which allows pernicious anemia and certain other defects in B₁₂ absorption to be treated with oral megadoses of B₁₂, even without any correction of the underlying absorption defects.^[70] See the section on supplements above.

The total amount of vitamin B₁₂ stored in body is about 2–5 mg in adults. Around 50% of this is stored in the liver. Approximately 0.1% of this is lost per day by secretions into the gut, as not all these secretions are reabsorbed. Bile is the main form of B₁₂ excretion; most of the B₁₂ secreted in the bile is recycled via enterohepatic circulation. Excess B₁₂ beyond the blood's binding capacity is typically excreted in urine. Owing to the extremely efficient enterohepatic circulation of B₁₂, the liver can store 3 to 5 years' worth of vitamin B₁₂;^[71] therefore, nutritional deficiency of this vitamin is rare. How fast B₁₂ levels change depends on the balance between how much B₁₂ is obtained from the diet, how much is

secreted and how much is absorbed. B₁₂ deficiency may arise in a year if initial stores are low and genetic factors unfavourable, or may not appear for decades. In infants, B₁₂ deficiency can appear much more quickly.^[72]

History

B₁₂ deficiency is the cause of pernicious anemia, an anemic disease that was usually fatal and had unknown etiology when it was first described in medicine. The cure, and B₁₂, were discovered by accident. George Whipple had been doing experiments in which he induced anemia in dogs by bleeding them, and then fed them various foods to observe which diets allowed them fastest recovery from the anemia produced. In the process, he discovered that ingesting large amounts of liver seemed to most rapidly cure the anemia of blood loss. Thus, he hypothesized that liver ingestion might treat pernicious anemia. He tried this and reported some signs of success in 1920.

After a series of clinical studies, George Richards Minot and William Murphy set out to partly isolate the substance in liver which cured anemia in dogs, and found that it was iron. They also found that an entirely different liver substance cured pernicious anemia in humans, that had no effect on dogs under the conditions used. The specific factor treatment for pernicious anemia, found in liver juice, had been found by this coincidence. Minot and Murphy reported these experiments in 1926. This was the first real progress with this disease. Despite this discovery, for several years patients were still required to eat large amounts of raw liver or to drink considerable amounts of liver juice.

In 1928, the chemist Edwin Cohn prepared a liver extract that was 50 to 100 times more potent than the natural liver products. The extract was the first workable treatment for the disease. For their initial work in pointing the way to a working treatment, Whipple, Minot, and Murphy shared the 1934 Nobel Prize in Physiology or Medicine.

These events led to discovery of the soluble vitamin, called vitamin B₁₂, from bacterial broths. In 1947, while working for the Poultry Science Department at the University of Maryland, Mary Shaw Shorb (in a collaborative project with Karl Folkers from Merck.) was provided with a \$400 grant to develop the so-called "LLD assay" for B₁₂. LLD stood for *Lactobacillus lactis* Dorner,^[73] a strain of bacterium which required "LLD factor" for growth, which was eventually identified as B₁₂. Shorb and colleagues used the LLD assay to rapidly extract the anti-pernicious anemia factor from liver extracts, and pure B₁₂ was isolated in this way by 1948, with the contributions of chemists Shorb,^[74] Karl A. Folkers of the United States and Alexander R. Todd of Great Britain. For this discovery, in 1949 Mary Shorb and Karl Folkers received the Mead Johnson Award from the American Society of Nutritional Sciences.^[74]




The chemical structure of the molecule was determined by Dorothy Crowfoot Hodgkin and her team in 1956, based on crystallographic data.^[75] Eventually, methods of producing the vitamin in large quantities from bacteria cultures were developed in the 1950s, and these led to the modern form of treatment for the disease.

See also

- Cobamamide
- Cyanocobalamin includes discussion of chemistry of preparation of reduced-cobalt B₁₂ analogues
- Hydroxocobalamin
- Methylcobalamin

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External links

- Jane Higdon, "Vitamin B12 (<http://ipi.oregonstate.edu/infocenter/vitamins/vitaminB12/>)", Micronutrient Information Center, *Linus Pauling Institute, Oregon State University*
- Cyanocobalamin (https://www.nlm.nih.gov/cgi/mesh/2011/MB_cgi?mode=&term=Cyanocobalamin) at the US National Library of Medicine Medical Subject Headings (MeSH)

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Categories: Organocobalt compounds | Cofactors | Vitamin B12 | B vitamins

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